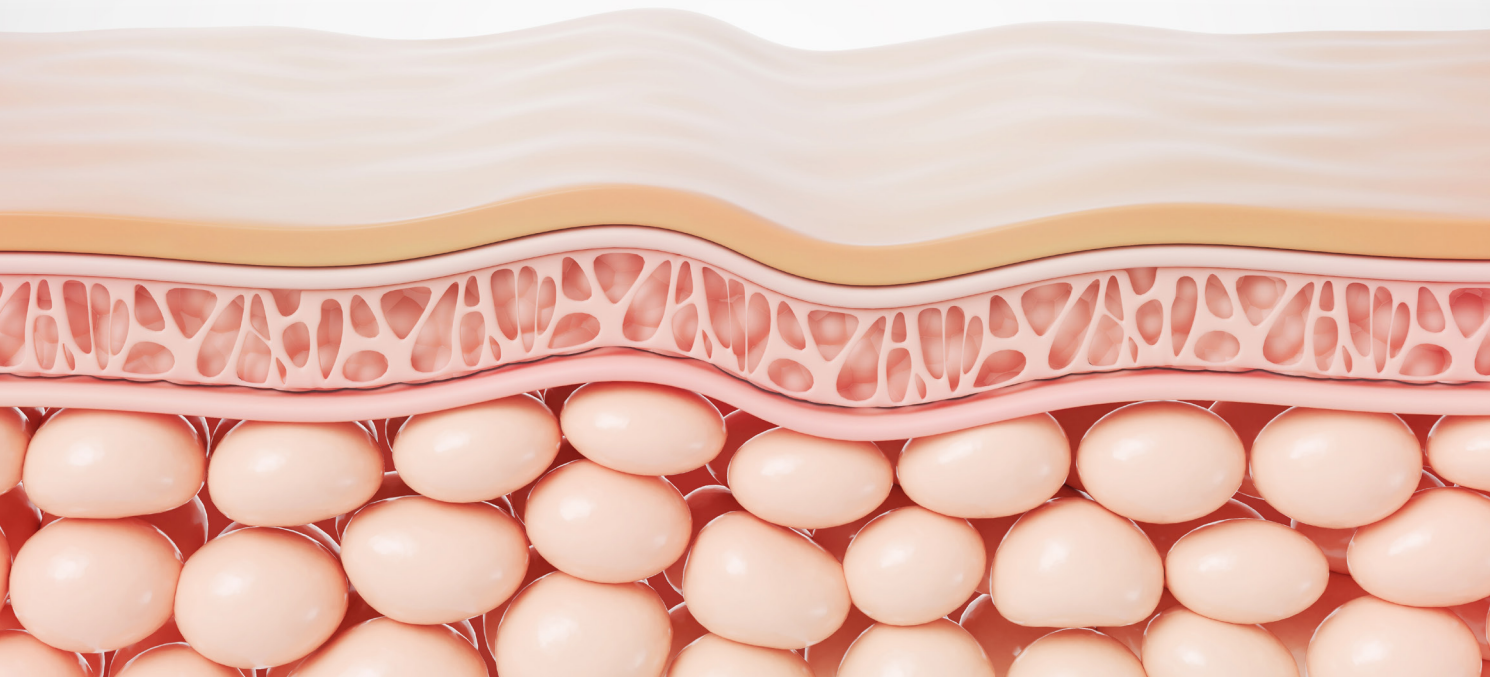
Türkiye Klinikleri

Contact Dermatitis

Kontakt Dermatit

Editor/Editör:
Prof. Dr. Suhan GÜNAŞTI TOPAL



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Contact Dermatitis

Kontakt Dermatit

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PREFACE ÖN SÖZ



We can define contact dermatitis as acute or chronic inflammation of the skin caused by exposure to chemical or physical agents. Contact dermatitis is an important dermatosis that accounts for more than 90% of all occupational skin diseases. Therefore, it negatively affects the quality of life and working efficiency. Curative treatment is to find the possible causative agent and eliminate it. In order to detect the causative agent, it is necessary to allocate time to the patients and to perform a detailed history, physical examination, patch test. However, the possible causative agent may not be detected.

Apart from allergic and irritant contact dermatitis, which are the two main types of contact dermatitis, subtypes such as early type reactions, photocontact dermatitis, systemic contact dermatitis, and non-eczematous contact dermatitis have also been described. Contact dermatitis is characterized by eczematous rashes of different stages, so it mimics various dermatological diseases such as dematophyte infections, cutaneous lymphoma, drug eruptions, nutritional deficiencies. It is also important to make a differential diagnosis.

We believe that this book will be a reference source for many of the problems we will encounter in our dermatology practice related to contact dermatitis. This book also outlines diagnostic procedures and testing methods -including patch testing- as well as treatment considerations. Dermatologists, family physicians, medical students, and residents will find this an essential reference.

I would like to thank the authors, Türkiye Klinikleri and its staff, each of whom contributed to the preparation of this book, each more valuable than the other, and who increased the value of this book with their knowledge.

Prof. Dr. Suhan GÜNAŞTI TOPAL
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ÖN SÖZ PREFACE



Kontakt dermatiti; kimyasal veya fiziksel ajanlara maruz kalmanın neden olduğu derinin akut ya da kronik inflamasyonu olarak tanımlayabiliriz. Kontakt dermatit, tüm mesleki cilt hastalıklarının %90'dan fazlasını oluşturan önemli bir dermatozdur. Bundan dolayı da hayat kalitesini, çalışma verimliliğini olumsuz etkiler. Küratif tedavisi, olası etkeni bulmak ve onu elimine etmektir. Etkeni saptamak için hastalara zaman ayırmak ve ayrıntılı öykü, fizik muayene, yama testi yapmak gerekir. Buna rağmen olası etken saptanamayabilir.

İki ana tip kontakt dermatit olan alerjik ve iritan kontakt dermatit dışında, erken tip reaksiyonlar, fotokontakt dermatit, sistemik kontakt dermatit, ekzematöz olmayan kontakt dermatit gibi alt tipleri de tanımlanmıştır. Kontakt dermatitler, faklı evrelerdeki ekzematöz döküntüler ile karakterizedir, bu yüzden de dematofit enfeksiyonları, kutanöz lenfoma, ilaç erüpsiyonları, beslenme yetersizlikleri gibi çeşitli dermatolojik hastalıkları taklit eder. Ayırıcı tanısının yapılması da önem arz eder.

Bu kitabın, kontakt dermatite bağlı dermatoloji pratiğimizde karşılaşacağımız birçok sorun için referans kaynağı olacağına inanıyoruz. Bu kitap aynı zamanda tanı prosedürlerini ve test yöntemlerini (yama testi dahil) ve tedaviyle ilgili hususları da özetlemektedir. Dermatologlar, aile hekimleri, tıp öğrencileri ve asistanlar bunu önemli bir referans olarak görecektir.

Bu kitabın hazırlanmasında emeği geçen her biri birbirinden kıymetli, bilgileri ile bu kitabın değerini artıran yazarlara, Türkiye Klinikleri ve çalışanlarına teşekkür ederim.

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Contact Dermatitis

Kontakt Dermatit

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Mechanisms in Irritant and Allergic Contact Dermatitis

İrritan ve Alerjik Kontakt Dermatitteki Mekanizmalar

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ABSTRACT Contact dermatitis can be in the form of irritant contact dermatitis (ICD), which occurs when the skin is exposed to irritants, or allergic contact dermatitis (ACD), which occurs when the skin is exposed to allergens. Today, there are many known allergens and especially irritants that individuals are exposed to occupationally. Although ICD and ACD reactions have similar clinical and histological features, they have differences in terms of pathogenesis. ICD occurs as a result of the activation of the innate immune system due to the direct cytotoxic effect of the irritant agent; prior sensitization is not required. ACD is a delayed hypersensitivity reaction in which allergen-specific T cells take part in the inflammatory process. In ACD, after sensitization with an allergen, dermatitis occurs with re-exposure to the same allergen. In both types of contact dermatitis, inflammatory reactions are limited by the anti-inflammatory mechanisms involved in the process.

Keywords: Dermatitis, irritant; dermatitis, allergic contact; haptens

ÖZET Kontakt dermatit, derinin irritanlarla maruziyetiyle oluşan irritan kontakt dermatit (İKD) veya alerjenlerle maruziyeti ile oluşan alerjik kontakt dermatit (AKD) şeklinde olabilmektedir. Günümüzde bilinen çok sayıda alerjen ve özellikle mesleki olarak maruz kalınan çok sayıda irritan madde bulunmaktadır. İKD ve AKD reaksiyonları klinik ve histolojik olarak benzer özelliklere sahip olmalarına rağmen patogenez bakımından farklılıklara sahiptir. İKD irritan ajanın direkt sitotoksik etkisiyle innate immün sistemin aktivasyonu sonucu oluşur, önceden duyarlılaşma gerekmez. AKD ise alerjen spesifik T hücrelerinin inflamatuar süreçte yer aldığı gecikmiş tip aşırı duyarlılık reaksiyonudur. AKD'de alerjenle duyarlılaşma sonrası, aynı alerjene tekrar maruziyet ile dermatit kliniği oluşur. Her iki kontakt dermatitte de sürece dahil olan anti-inflamatuar mekanizmalarla inflamatuar reaksiyonlar sınırlandırılır.

Anahtar Kelimeler: Dermatit, irritan; dermatit, alerjik kontakt; haptenler

Contact dermatitis is an inflammatory skin reaction that occurs when the skin is exposed to irritants or allergens.[1] Irritant contact dermatitis (ICD), which develops as a result of the direct cytotoxic effect of a chemical or physical agent, constitutes approximately 80% of all contact dermatitis, and the remainder consists of allergic contact dermatitis (ACD) caused by allergen contact.[2,3] ICD and ACD (especially in their chronic forms) can have similar clinical appearances. The classic clinical appearance of contact dermatitis is erythematous, scaly, vesicular patches or plaques in the area corresponding to the contact area.[3] While ICD and ACD are often indistinguishable clinically and histopathologically, the most important difference in ACD in terms of inflammatory pathways is the involvement of allergen-specific T cells in the process, while in ICD the inflammatory reaction mainly depends on chemical and/or physical irritation.[1] In this section, the pathogenesis mechanisms in the formation of ICD and ACD reactions are discussed.

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IRRITANT CONTACT DERMATITIS

ICD is a cutaneous inflammatory reaction resulting from the activation of the innate immune system by the direct cytotoxic effect of a chemical or physical agent. Although it has different pathogenesis, it causes similar clinical findings to ACD, especially in chronic forms. In acute cases, erythema, scale, edema, and vesiculation are observed, while in chronic cases, lichenification, hyperkeratosis, and fissures are observed. Strong irritants can cause chemical burns with necrosis and ulceration.[2]

ICD is the most common form of contact dermatitis and the most common occupational skin disease.[4] It is more common in occupational groups such as healthcare workers, cleaners, food industry workers, hairdressers, metal workers, chemical industry workers, and construction workers, especially those who engage in wet work and come into contact with many irritants.[4,5] Some of the irritant chemicals such workers are exposed to include acids (inorganic and organic), alkalis (e.g., potassium hydroxide, sodium carbonate), solvents (e.g., benzene, toluene, gasoline), alcohol, detergents, disinfectants (e.g., aldehydes, halogens, ethylene oxide), metal salts, plastics, food- and plant-derived chemicals, water, and body fluids.[2]

PATHOGENESIS

Irritant contact dermatitis (ICD) is a cutaneous reaction that occurs when skin damage caused by exposure to irritating chemical and physical agents leads to skin barrier disorder, cellular changes, and the release of pro-inflammatory mediators.[6] Since prior sensitization is not required for the development of ICD, ICD can develop in anyone who comes into contact with the irritant at a sufficient dose and duration. It occurs at first contact with strong irritants such as acids and bases.[5] Clinical symptoms occur with cumulative damage to the skin barrier through repeated contact with weak irritants such as water and soap. In addition to chemical irritants, ICD can also occur with physical irritations such as friction and abrasion of the skin, as seen in construction workers.[7]

ICD, which was previously believed to be a monomorphic process, is now accepted to be a complex process with a different pathophysiology and natural course.[6] Disruption of the skin barrier, epidermal cellular changes, release of pro-inflammatory mediators, and activation of the innate immune system are the mechanisms responsible for the development of ICD.[7,8] Unlike allergic skin reactions, immunological memory does not play a role in ICD, and its development does not require prior sensitization.[9]

The skin is an effective barrier that protects the organism from pathogens, chemicals, and physical effects and prevents water loss. The physical barrier of the skin consists mainly of the stratum corneum. The stratum corneum is a layer consisting of corneocytes embedded in an intercellular matrix consisting of a lamellar lipid layer. The major lipids of the stratum corneum are ceramides, free fatty acids, and cholesterol.[10] Lipids prevent water loss and limit the penetration of applied substances. Exposure to irritants causes damage to the stratum corneum and disrupts the skin barrier.[6] Various irritating substances can cause skin damage through a variety of toxicity mechanisms such as direct cytotoxic effect, protein denaturation, solubilization of membrane lipids, and barrier lipid denaturation.[2] For example, while the irritating substance sodium lauryl sulfate (SLS) found in detergents is directly toxic to epidermal keratinocytes, an organic solvent such as acetone also causes disruption of the skin barrier through lipid loss.[11] Skin barrier integrity can be assessed by measuring transepidermal water loss (TEWL). If the skin barrier is disrupted, there is an increase in TEWL.[8] In research using the anionic surfactant SLS, application of SLS to the skin has been shown to cause disruption of the skin barrier and increase TEWL measurements. Disruption of the skin barrier also facilitates the penetration of irritants themselves, as well as allergens and bacteria, into the skin.[9]

In the acute phase of ICD, the pathogenic pathway is common to many irritants: penetration of irritants into the stratum corneum, mild damage to keratinocytes, release of inflammatory mediators, and T cell activation.[2] In the acute phase, irritants penetrate the stratum corneum and directly activate epidermal keratinocytes.[6] Keratinocytes play a major role in the immune response to irritants. Keratinocytes release cytokines on disruption of the skin barrier and upregulate the expression of major histocompatibility class II antigens and cell adhesion molecules.[12] The innate immune system is activated by the release of pro-inflammatory cytokines such as interleukin (IL)-1α, IL-1β, tumor necrosis factor (TNF)-α, granulocyte macrophage colony-stimulating factor (GM-CSF), IL-6, and IL-8 from keratinocytes.[11] TNF-α and IL-1α are the major mediators. These induce the production of other cytokines, chemokines, and adhesion molecules, leading to the recruitment of leukocytes.[2] TNF-α works together with IL-1α and IL-1β to activate T cells, perpetuate cytokine and chemokine production, and upregulate intercellular adhesion molecule-1 (ICAM-1), which is a characteristic feature of ICD. TNF-α and IL-1α also trigger the release of chemokines CCL20 and CXCL8, which attract mononuclear and polymorphonuclear cells to the

site of irritation.[6] IL-6, IL-8, and GM-CSF activate Langerhans cells, dermal dendritic cells, and endothelial cells.[4] In ICD, the chemokine CCL21 produced by dermal lymphatic endothelial cells is upregulated and facilitates naive T lymphocyte migration. T lymphocytes entering the area of irritation often express cutaneous lymphocyte-associated antigen (CLA), which is involved in transendothelial T lymphocyte migration.[12] With the recognition of irritants as danger signals by Toll-like receptors (TLR) and NOD-like receptors, the inflammasome and nuclear factor-κB (NFκB) pathway is activated. Chemokines released from these cells cause the recruitment of neutrophils, lymphocytes, macrophages, and mast cells to the epidermis.[11] As a result, clinical symptoms of acute ICD (dryness, redness, edema, and vesiculation) occur. Acute ICD usually develops as a result of a single exposure to an irritant. Symptoms often disappear within days to weeks.[9] In this process, anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist (IL-1RA) are produced to counteract inflammation, limiting the inflammatory process.[13,14]

The mechanism of development for chronic ICD, which develops with repeated exposure of the skin to mild irritants, and the factors that predispose the individual to it are not sufficiently understood.[13] Chronic ICD may occur due to various factors such as the nature of the irritating substance or genetic and environmental factors.[15] The sometimes observed chronicity of ICD has two possible immunological explanations: first, irritant-induced inflammation results in a priming of the immune system to its self-immunogenic skin peptides, leading to chronic inflammation; second, TNF-α production from keratinocytes triggered by irritants is regulated in an autocrine manner and thereby maintains the inflammatory environment.[12,15] Thus, the ICD reaction can continue for years.[9] In the chronic phase of ICD, the barrier function of the stratum corneum is disrupted. Desquamation and increased TEWL occur. TEWL stimulates lipid synthesis, keratinocyte proliferation, and hyperkeratosis in the repair of the skin barrier. After chronic exposure to irritants, there is an increase in epidermal turnover, which is seen clinically as a chronic eczematoid reaction.[2] Chronic (cumulative) ICD is clinically manifested by dryness, redness, scaling, and fissuring. It is usually localized in the hands. It is chronic; the clinical reaction may continue for several years despite removal of irritant exposure.[9] In most cases, although exposure to the irritant continues, ICD resolves and individuals can continue their work. This condition, called "hardening phenomenon" or "accommodation", is the adaptation of the skin to the irritating substance. Hardening is the condition in which chronic ICD is avoided despite continued exposure to the irritant. The mechanism of this hardening phenomenon is still not fully understood.[15] With repeated exposure to irritants, there is an initial increase in TEWL which then decreases as contact continues, indicating hardening. Upregulation of the production of ceramide 1, an important component of stratum corneum lipids, with repeated exposure plays an important role in protection from irritation.[12] In their study of repeated SLS application in 23 non-atopic volunteers, Heinemann et al. showed that TEWL increased in the first 2 weeks but decreased in the third week (an effect of adaptation) and was accompanied by a significant increase in ceramide 1. They proposed that upregulation of ceramide 1 synthesis may play a major role in the development of the hardening effect.[16] One of the possible mechanisms in the hardening phenomenon is the physical change in the skin barrier, as a hyperkeratotic stratum corneum and thick stratum granulosum layer reduce the penetration of irritants.[17] In addition, changes in the expression of inflammatory mediators are among the other changes seen in hardened skin.[15]

ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis (ACD) is a T cell-mediated delayed-type hypersensitivity reaction triggered by skin contact with the relevant chemical in an individual who has previously been sensitized to the same chemical. Clinically, it presents with itchy eczematous lesions.[18] The number of contact allergens known today is approximately 5000. The most common sensitizing contact allergens can be classified as metals (e.g., nickel, cobalt, chromium), cosmetic products (e.g., fragrances, preservatives, paraphenylenediamine), rubber compounds, adhesives and resins, textile products, topical agents, and plants.[19]

The pathogenesis of allergic contact dermatitis is a two-phase process. The sensitization phase begins with first contact with the hapten and results in the production of effector T cells, and the elicitation phase develops with re-exposure to the allergen, producing dermatitis.[20]

HAPTEN

The binding of hapten is the first step in the development of allergic contact dermatitis. Most contact allergens are chemicals called haptens with a molecular weight of less than 500 daltons that can penetrate the stratum corneum layer of the skin. Haptens are not immunogenic by themselves, but when they bind to a nonspecific skin protein called the carrier, they form a hapten-carrier-complex, only in this way can they be recognized by the immune

system.[18] For example, the poison ivy allergen binds covalently to protein nucleophilic groups, while metal ions (e.g., nickel) form stable metal-protein chelate complexes.[21] Some of the allergens are converted into protein-reactive molecules by metabolic transformation or oxidation by epidermal keratinocytes and/or dendritic cells, which are called "pro-hapten." If the hapten requires activation outside the skin by means such as oxidation, this hapten is called "pre-hapten".[18] Allergenicity depends on the physicochemical properties of the haptens, such as their penetrating power into the stratum corneum layer, lipophilicity, and chemical reactivity, as well as their proinflammatory activity and capacity to induce maturation of Langerhans cells.[21]

SENSITIZATION PHASE

The sensitization phase occurs at the first contact of the skin with the hapten and leads to the formation of hapten-specific T lymphocytes in the regional lymph nodes and their migration to the skin. This activity is also known as the afferent phase or the induction phase.[22] After penetrating the stratum corneum, the hapten conjugates to self-protein or amino acids. This hapten-protein complex acts as an allergen that stimulates the immune system.[23] Upon contact of the allergen with the skin, professional antigen-presenting cells (APC) are involved in the process. The best defined antigen-presenting cells in the skin are langerhans cells (LC) and dermal dendritic cells (dDC). APCs are cells of the innate immune system, but they play a key role in the initiation of adaptive immune reactions.[18] Langerhans cells (LCs) are the major dendritic cell population in the epidermis. LCs form a dense network in the epidermis, constantly scanning the environment by expanding and retracting their dendrites. Thus, they can detect a pathogen that has breached the skin barrier.[24] LCs receive the antigen, transport this antigen to the lymph nodes draining the skin, and during this migration, they undergo a maturation process where they process the antigen and present it in the context of a major histocompatibility complex (MHC) class I and class II proteins.[24] In the lymph node, APCs presenting antigens through MHC class I and class II, activate naive CD8+ and CD4+ T cells, respectively. This leads to priming and clonal expansion of antigen-specific T cells. Through this activity, APCs initiate the adaptive immune response.[25]

In sensitization, the direct association of haptens with MHC molecules in Langerhans cells is very important. Lipophilic haptens directly penetrate the LC, conjugate with cytoplasmic proteins and are presented by the MHC class I molecule through endogenous route processing of the antigen, while hydrophilic allergens (e.g., nickel), after conjugating with skin proteins, are presented by the MHC class II through exogenous route processing of the antigen. Thus, the chemical nature of the haptens may determine the activation state of CD8+ and/or CD4+ T cells.[21] In systemic hapten exposure, organ-specific antigen-presenting cells, such as Kupffer cells in the liver, get involved.[18]

After the sensitizers contact the skin, about 40% of the epidermal LCs are activated. They leave the epidermis and migrate to the draining lymph nodes via afferent lymphatic vessels.[21] If we look at this migration process, IL-1β release from LC is induced within 15 minutes after exposure to the hapten. IL-1β stimulates the release of TNF-α and GM-CSF from keratinocytes. IL-1β and TNF-α reduce membrane-bound E-cadherin expression, thus enabling the separation of LC from surrounding keratinocytes. In addition, the production of matrix metalloproteinases, which break down the basement membrane, increases, and expression of adhesion molecules that enable interaction with the extracellular matrix and dermal cells occurs. In this way, the migration of Langerhans cells from the epidermis to the lymphatics is facilitated.[21] During migration, LCs undergo a maturation process and acquire the mature dendritic cell (DC) surface phenotype. In mature DCs, increased expression of CD83 (a marker of DC maturation) is observed, as well as adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1); co-stimulatory molecules such as CD40, CD80, CD86; and chemokine receptors such as CCR7.[18] In particular, CCR7 expression guides mature LCs to afferent lymphatics and the paracortical area of the lymph node.[21] Because both lymphatics and high endothelial venules produce CCL21, the ligand of CCR7. As a result, CCR7-CCL21 interaction plays a very important role in the migration of LCs to the paracortical region of the lymph node, which is rich in T cells.[26] Hence, induced expression of CCR7 with the maturation facilitates the contact of antigen-loaded DCs with naive T cells in the paracortical lymph node area.[18,26] The regulation of DC maturation markers is specific to immune response-stimulating antigens; skin irritants do not cause similar changes in LC surface markers.[18] Haptenized LCs migrating to the lymph node further mature, and their increased dendritic morphology facilitates multiple cell contact, leads to the binding and activation of allergen-specific T cells.[21] In the lymph node, APC antigen presentation through MHC class I and class II, activates naive CD8+ and CD4+ T cells, respectively.[25]

Activation of allergen-specific T cells begins when MHC-allergen complexes presented on the surface of APCs in the lymph node bind to the T-cell receptor (TCR) on the T lymphocyte surface, forming the first signal in T cell activation.[21] Then, this activation is strengthened by secondary signals provided by cellular adhesion molecules on the cellular membrane of APCs, T cells, and cytokines (IL-1).[1] This activation cascade is characterized by the mutual activation of APCs and hapten-specific T lymphocytes. Activation protects APCs from apoptotic death, prolonging their life. With activation, naive allergen-specific T cells start to produce various cytokines, especially IL-2, which is a T cell growth factor and at the same time IL-2 receptors are upregulated in T cells. In this way, a positive feedback loop is provided, resulting in up to 1000-fold clonal expansion of T cells. This proliferation process can sometimes appear as painful lymph node swelling.[1] As a result, naive T lymphocytes are activated and differentiate into allergen-specific effector cytotoxic T lymphocytes (Tc) and effector T helper lymphocytes (Th).[27] Polarization of primed CD4+ and CD8+ T lymphocytes occurs depending on the secreted cytokines in the DC-T cell interaction. T cells are polarized as Type 1 cells (producing interferon (IFN)-γ, IL-2 and TNF-α), Type 2 cells (producing IL-4, IL-10, IL-13, and IL-5), or Type-17 cells (producing IL-17A, IL-17F, IL-21, and IL-22). The mechanisms responsible for polarization are not fully understood and depend on the DC subset type, the nature of the antigen, and the factors released by the tissue microenvironment.[22] Subtypes of CD4+ and CD8+ T cells (Th1/Tc1, Th2/Tc2, and Th17/Tc17) are involved in the cutaneous immune response.[28] Type 1 T cell polarization is crucial to the development of specific effector T cells and ACD reactions.[22] In ACD, in many instances the most important effector cells are CD8+ Tc1 lymphocytes.[29] The classical cell of the delayed-type hypersensitivity reaction is CD4+ T cells. However, the major effector T cells in ACD are CD8+ T lymphocytes. This has been demonstrated in mouse models when depletion of CD8+ cells results in a significant reduction in contact hypersensitivity reactions.[25]

Various studies have shown that antigen contact alone is not sufficient to develop sensitivity to an antigen.[19] For the initiation of the immune response and sensitization, the presence of danger signals derived from endogenous or exogenous sources together with the antigen is required. If there are no danger signals in the environment, it is thought that allergen contact does not cause sensitization but results in immunological tolerance. Many contact allergens are both antigenic and can produce danger signals. The formation of danger signals is related to the irritant properties of the allergen and occurs when it causes cell and tissue damage.[30] Contact allergens induce intracellular stress in epidermal cells by causing the release of danger signals called damage-associated molecular patterns (DAMPs), such as reactive oxygen species (ROS), hyaluronic acid fragments, and damaged extracellular matrix proteins (fibronectin, hyaluronan, and β-defensins).[27,30] DAMPs are recognized by Toll-like receptors (TLR) and NOD-like receptors (NLR) on dendritic cells.[27] Stimulation of TLR2 and TLR4 by DAMP molecules leads to the expression of the proinflammatory cytokines IL-1β, TNF-α, IL-18, IL-6, IL-12, IL-23, and IFN-α, thus providing a danger signal. IL-1β and TNF-α are essential for the maturation and migration of APCs.[30] On the other hand, less potent allergens cannot form the danger signal on their own and require exogenous proinflammatory stimuli. They become sensitizers if there is a condition that increases proinflammatory cytokines in the skin area where they are applied, such as infection, irritation, or trauma. For example, while some topical antibiotics have very weak sensitizing potential, they act as contact allergens when applied to inflamed skin, such as a leg ulcer, where danger signals already exist.[19,30]

Keratinocytes, other cells involved in the development of ACD, secrete cytokines such as IL-1β, TNF, and IL-18. These cytokines are important in the maturation and migration of DC. Additionally, keratinocytes can respond to hapten with the TLRs they express.[28] During the sensitization phase, along with keratinocytes and dendritic cells, neutrophils, mast cells, natural killer (NK) cells, and gamma delta T cells also play roles in the immune response.[19]

By the end of the sensitization phase, hapten-specific effector/memory T lymphocytes are formed and are distributed to the skin, lymph nodes, and vessels.[23] Thus, immunological memory is established and the sensitization phase is concluded.[27] The sensitization phase lasts 10–15 days and clinical findings are not observed in the majority of cases. However, it has been shown that ACD may develop 5–15 days after the first skin contact with a strong hapten in previously nonsensitized individuals. This condition is called Primary ACD. The pathophysiology of this condition is the same as classical ACD, and since the hapten remains in the skin for a long time, it can be induced after a single skin contact.[22]

ELICITATION PHASE

Re-exposure of a sensitive individual to the same hapten causes clinical manifestations of allergic contact der-

matitis within 24-72 hours. This process is called the "elicitation phase", or the "efferent phase". This phase is mediated by hapten-specific T cells.[22] Upon re-exposure to the same antigen, hapten-specific T cells are activated and recruited in the skin, and a delayed-type hypersensitivity reaction is formed.[18,25] At this stage, the recruitment of activated T cells causes epidermal tissue destruction, such as erythema, vesicles, and blister formation.[25]

In resting skin after sensitization, few skin-homing CLA+ T cells are present.[21] Upon recontact of haptens with the skin, the haptens penetrate the epidermis and react with endogenous proteins (as in the sensitization phase). Hapten-protein complexes are taken up by APCs and presented to antigen-specific T cells located in the epidermis and dermis. Pro-inflammatory cytokines, such as IL-1β, TNF-α and IL-18, are released from hapten-stimulated LCs and keratinocytes.[18] These cytokines activate vascular endothelial cells and increase the expression of adhesion molecules (ICAM-1 and P/E selectin), which enable the migration of T lymphocytes in the blood to the tissue. Haptens increase vascular permeability through the release of histamine from mast cells.[28] Keratinocytes also secrete chemokines (e.g., CXCL9/10, CCL17, CCL20, CCL27) that attract T lymphocytes to the site. Activated T lymphocytes present cutaneous lymphocyte-associated antigen (CLA), very late antigen (VLA)-4, and chemokine receptors. CLA binds to E-seletin expressed in the endothelium, and VLA-4 binds to vascular cell adhesion protein (VCAM)-1, initiating the transition of the T cell from the vascular to the tissue.[18] When haptens stimulate the release of DAMPs, TLRs are stimulated and proinflammatory cytokines are released. Cytokines induce the recruitment of Th1 and Th17 cells. Th1 cells produce the DAMP molecule extradomain A+ fibronectin, which is an endogenous ligand of TLR4. DAMPs also increase stimulation of TLRs. Thus, a positive feedback is formed that will further strengthen the innate and adaptive immune activation.[30]

Effector T lymphocytes produce inflammatory cytokines, especially IFN-γ, IL-1α, IL-6, IL-17, IL-26, TNF-α, and IL-23, at the site of inflammation, leading to further recruitment of cytotoxic T lymphocytes and innate immune system cells.[25] In keratinocytes stimulated by IFN-γ, adhesion molecules, cytokines, and chemokines are upregulated, which enables the recruitment of more T lymphocytes, macrophages, NK cells, mast cells, and eosinophils. Both CD4+ and CD8+ T cells mediate the inflammatory response, but the main effector cells that first enter the skin are CD8+ cells. The function of hapten-specific CD4+ T cells is not fully understood.[18] CD8+ cells have proinflammatory functions, while CD4+ cells have proinflammatory and anti-inflammatory functions depending on their subtype.[28] In recent years, studies have revealed the contribution of the innate immune system and B cells in the recruitment of hapten-specific T cells at the allergen site. After contact with the hapten, natural killer T cells (NKT) are stimulated. NKTs promote the B1-like B-cell subtype and their production of hapten-specific immunoglobulin M (IgM) antibodies. IgM binds the hapten antigen and stimulates complementary formation of C5a. C5a stimulates the release of vasoactive serotonin and TNF-α from mast cells and platelets, leading to local vascular activation and recruitment of effector T cells. Subsequently, the inflammatory response is strengthened with the secreted cytokines and chemokines, and leukocyte infiltration occurs. Neutrophil density is related to the number of antigen-primed CD8+ T cells recruited at the cutaneous area.[22]

In the early phase of ACD, tissue damage is mainly due to apoptosis of keratinocytes carrying the hapten on MHC class I molecules, triggered by CD8+ T cells. Apoptosis is mediated by the perforin/granzyme or Fas/Fas Ligand pathways. Keratinocyte apoptosis is accompanied by cleavage of intercellular adhesion molecules. Infiltration of lymphocytes into the epidermis, loss of intercellular adhesion, intercellular edema, and vesiculation lead to a typical spongiotic appearance in the epidermis. This inflammatory response to eliminate antigen-modified keratinocytes, results in desquamation. Desquamation contributes to the removal of the antigen.[18] The efferent phase lasts 72 hours and then decreases rapidly with down-regulatory mechanisms.[22]

REGULATORY MECHANISMS

It appears that numerous regulatory mechanisms suppress the inflammation to avoid tissue damage. The release of anti-inflammatory cytokines, activation of regulatory T cells (Tregs) with down-regulatory properties, and elimination of antigen-loaded DCs by effector CD8 + T cells are among these mechanisms.[22] Regulatory T cells (Tregs) are a heterogeneous subset of T lymphocytes. They suppress the immune response through the release of anti-inflammatory cytokines or by deactivating effector T cells. In response to antigenic recognition, they accumulate in the tissue where the antigen is located and suppress the proliferation and activation of CD4+, CD8+ T cells, NK cells, and APCs.[28] These cells can be classified as inducible

Tregs (Tr1 and Th3 cells) and natural Tregs (CD4+CD25+Foxp3+ cells). The skin contains mainly inducible Tregs.[18] Tregs exercise their regulatory effects through the secretion of soluble suppressive factors, especially IL-10, as well as contact dependent mechanisms such as CD39/CD73 and granzyme/perforin. These cells also inhibit leukocyte influx into the skin.[31] As a result, Tregs may be involved in controlling and terminating the inflammatory process in ACD.[18]

LOCAL SKIN MEMORY

In former allergic contact dermatitis sites, a few residual hapten-specific T cells can remain in close proximity to dermal dendritic cells. These cells form local skin memory.[21] Memory T cells in the skin are strategically positioned as the first line of defense against re-exposure to antigens.[28] Upon renewed allergen contact to the site of the former skin reaction, these cells can cause a "flare-up" reaction that peaks within a few hours.[21]

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Immediate Contact Reactions: Pathomechanisms and Clinical Presentation

Ani Temas Reaksiyonları: Patomekanizma ve Klinik Bulgular

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ABSTRACT Immediate contact reactions comprise allergic and nonallergic inflammatory reactions of the skin or mucous membranes including contact urticaria, contact urticaria syndrome, and protein contact dermatitis. They frequently start within 30-60 min following skin exposure of causative agent and clear completely within 24 h. However, delayed onset reactions may occur within 4-6 h. Type I hypersensitivity reactions or non-immunological mechanisms play a role in pathogenesis. In dermatology practice, immediate contact reactions are common but are frequently underdiagnosed and/or misdiagnosed.

Keywords: Dermatitis, contact; urticaria; hypersensitivity, immediate; immunologic factors

ÖZET Ani temas reaksiyonları, kontakt ürtiker, kontakt ürtiker sendromu ve protein kontakt dermatit dahil olmak üzere deri veya mukozal alanların alerjik ve alerjik olmayan inflamatuar reaksiyonlarını içermektedir. Çoğunlukla bu reaksiyonlar sorumlu ajana temas sonrası 30-60 dakika içinde başlayıp, 24 saat içinde tamamen kaybolur. Bununla birlikte geç başlangıçlı reaksiyonlar 4-6 saat içinde ortaya çıkabilir. Tip I aşırı duyarlılık reaksiyonları veya immünolojik olmayan mekanizmalar patogenezde rol oynamaktadır. Dermatoloji pratiğinde ani temas reaksiyonları yaygındır ancak sıklıkla eksik ve/veya yanlış teşhis edilebilmektedir.

Anahtar Kelimeler: Dermatit, temas; ürtiker; aşırıduyarlılık, ani; immünolojik faktörler

Immediate contact reactions contain a heterogeneous group of both allergic and nonallergic inflammatory reactions of the skin or mucous membranes. Contact urticaria, contact urticaria syndrome (CUS), and protein contact dermatitis (PCD) are diseases which are precipitated by immediate contact skin and mucous membrane reactions. Immediate contact reactions are common in dermatology practice and are frequently overlooked.[1-3]

Currently available information is frequently obtained from occupational registrations, and there is not enough epidemiologic data on contact urticaria or PCD incidence in the general population. Prevalence of occupational contact urticaria in European healthcare professionals are thought to be between 5 and 10%, while data on occurrences in the general population vary between 1 and 3%.[3] Contact urticaria and protein contact dermatitis constituted 11% of all recognized cases of occupational skin diseases in the study period 2005-2016 in Finland.[4] In a tertiary-level specialist occupational dermatology clinic in Australia, 151 cases of contact urticaria were diagnosed over the 12-year period (1993-2004), and occupational contact urticaria was diagnosed in 8.3% (143 of 1720) of the total number of patients with occupational skin disease.[5] Using data for the period 2001-2010 from a French national network, 251 cases of occupational contact urticaria were reported.[6] In a study conducted between 2014-2015 at İstanbul Oc-

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cupational Disease Hospital, 56 patients were diagnosed with occupational dermatosis. Allergic contact urticaria was detected in 3 of these patients.[7]

Immediate contact reactions usually start within 30 to 60 minutes and clear completely in 24 hours, after external contact with a causative substance. Delayed-onset reactions may also occur within 4-6 hours. Inflammatory reactions including wheal, flare, and transient eczematoid erythema can be itch, tin, or burn. Non-immunological mechanisms or type I immediate hypersensitivity can cause these symptoms. The most common causes of milder reactions include fruits, vegetables, and cosmetics. Strong allergies can result in gastrointestinal symptoms, rhinoconjunctivitis, bronchial asthma, and even death.[2,8]

In this article, the pathomechanisms and clinical presentation of immediate contact reactions have been reviewed.

CONTACT URTICARIA

The term 'contact urticaria' was first described by Fisher in 1973.[1,3,9] Contact urticaria is not uncommon, and an ever-expanding list of causes, ranging from simple chemicals to macromolecules has been reported. Most compounds which induce these reactions due to plants, vegetables, food, and well-defined chemicals in many topical drugs, cosmetics, and toiletries. Both high and small molecular weight substances have the ability to cause contact urticaria.[1,10]

PATHOMECHANISM

According to the underlying mechanism contact urticaria is classified as:

1. Non-immunological contact urticaria (NICU)/irritant
2. Immunological contact urticaria (ICU)/allergic
3. Mixed or undetermined contact urticaria

1. Non-immunological contact urticaria

Non-immunological contact urticaria (NICU) is the commonest form of contact urticaria. It does not include immunological processes and causes a reaction in the majority of exposed individuals without any prior sensitization.[8,9] Especially, NICU is mainly mediated by a variety of small molecular compounds. Among these are benzoic acid, dimethyl sulfoxide, cinnamic acid, cinnamic aldehyde, ammonium persulfate, nicotinic acid esters, eugenol, and sorbic acid. Among fragrances, cinnamic aldehyde, cinnamic alcohol, isoeugenol, hydroxycitronellal, and geraniol might cause NICU.[1,8,11] However, the best example remains contact urticaria due to the stinging nettle (Urtica dioica).[3,12]

The pathogenesis of NICU is not clearly understood. A solitary contact with the causative substance may directly trigger the reaction.[3,12] These effects can be explained by at least three different mechanisms: nonspecific histamine release, modification of arachidonic acid metabolism, and stimulation of cutaneous nerves containing mediators like substance P.[1] Direct activation of mast cells, resulting in release of histamine and possibly the release of other vasoactive substances such as substance A, bradykinin, prostaglandins, and leukotrienes are believed to cause the reaction.[13] However, histamine is not thought to be a major factor due to the inefficacy of antihistamines. Nonsteroidal anti-inflammatory medications can suppress non-immunological urticarial reactions when used topically or orally, although antihistamines like terfenadine do not inhibit most of these reactions. It is interesting to note that ultraviolet radiation can stop this process.[1,14]

2. Immunological Contact Urticaria (ICU)

Immunological contact urticaria (ICU), is a type I hypersensitivity reaction mediated by allergen-specific IgE and requires previously sensitization. This condition is less common than NICU in clinical practice. It's mechanism is better understood. The pathogenesis is the same as other types of immediate hypersensivity reaction, involving the coupling of specific IgE molecules on the surface of mast cells with percutaneously absorbed antigens. The mast cell degranulation is induced and this leads to the release of histamine, which causes the symptoms.[1,2,8] Other mediators such as prostaglandins, leukotrienes, and kinins may also be involved.[2] ICU may be caused by two types of substances. The former group involves high molecular weight proteins (10,000 kD or more), whereas the second group involves hapten chemicals of low molecular weight (less than 10 kD).[12] This condition may be favored by pre-existing disorders, such as atopic dermatitis.

The primary example of ICU is natural rubber latex, for which thirteen distinct allergenic proteins have been identified, named hevein (Hev) b1 to b13. Since latex allergic people have a significant degree of cross-reactivity to other antigens, notably those found in fruits (banana, kiwi, avocado, and chestnut), allergy to natural rubber latex has wider consequences for affected patients; this condition is frequently called to as "latex-fruit syndrome".[12,15]

3. Mixed or undetermined contact urticaria

There is a third classification for agents that cause NICU and ICU-like symptoms together, or if the exact mechanism is still unknown. A well-known example is the

bleaching chemical ammonium persulphate, which can cause vascular collapse as well as localized and widespread reactions. Though the clinical picture suggests an IgE-mediated response, these antibodies against ammonium persulphate have not been found.[9]

The differences between ICU and NICU were shown in Table 1.[16]

CLINICAL PRESENTATION

Clinically, contact urticaria is identified by a threefold response that typically manifests as skin itching, wheal, and flare at the site of contact with the eliciting substance. The lesion develops within 30 minutes after the exposure and disappears entirely in a few hours, but not more than 24 hours, without residual signs and symptoms. The triple response can develop alone or in association with an immediately induced erythema, which can occur if the antigen exposure persists.[1-3] In Kligman's et al study, agents that cause wheals at a high concentration will almost always induce only erythema when a non-urticariogenic dilution, a variable percentage of individuals may experience pruritus alone.[10] NICU manifests with skin lesions usually being localized to the site of contact without previous sensitization, and systemic manifestations are infrequently seen. The urticaria of ICU can be limited to the contact areas, but sites other than the contact area can be affected.[1-3,12] Repeated exposure to the antigen may cause to gradually worsening of symptoms. Concomitant history of other atopic disorders like eczema, hay fever, and personal or family history of asthma is a risk factor for ICU.[17]

The term of 'contact urticaria syndrome' (CUS) was described in 1975 by Maibach and Johnson.[18] CUS is one of the type of the urticaria with a range of symptoms, both local and systemic, which can manifest in many different clinical presentations of contact urticaria, but it is most frequently seen in those who have ICU.[19] Patients and healthcare professionals may not be aware of CUS, which might lead to frequent underdiagnosis or misdiagnosis. In order to manage it, prevention and early detection are still crucial.[12] There have been reports of CUS following exposure to a wide range of chemicals, including pharmaceuticals, industrial contactants, foods, animals, plants, proteins, textiles, cosmetics, and physical agents including light, heat, cold, and water.[20] CUS is staged according to the occurrence of cutaneous and extracutaneous findings (Table 2).[1,12,20]

According to the causes of contact urticaria reported in literature, contact urticaria due to cosmetic products may

TABLE 1: The comparison of immunologic contact urticaria and non-immunologic contact urticaria.[9,13,16]

	Immunologic contact urticaria (ICU)	Non-immunologic contact urticaria (NICU)
Reaction type	Type I hypersensitivity reaction	Non-immunologic reaction
Previous sensitization	Yes	No
Mediator	Allergen specific IgE Histamine	Vasoactive substances such as histamine, substance A, bradykinin, leucotrienes, prostaglandins, ecosanoids
Elicitation time	10-20 min	<45 min
Systemic involvement	Occasionally associated; Contact urticaria syndrome Anaphylactic shock	None/Rarely Mainly presents as localized urticarial reactions
Severity of symptoms	More severe disease	Less severe disease
Inhibitor	Antihistamine	Nonsteroidal anti-inflammatory drugs

TABLE 2: Stages of contact urticaria syndrome.

Stage 1	Macular ertyhema or localized urticaria (redness, swelling); immediate contact dermatitis (protein contact dermatitis) Itching, tingling, or burning sensation
Stage 2	Generalized urticaria sometimes associated with angioedema
Stage 3	Multiple organ involvement; rhinoconjunctivitis, bronchial asthma, angioedema and orolaryngeal symptoms (lip swelling, hoarseness, swallowing difficulty), or gastrointestinal symptoms (nausea, vomiting, diarrhea, cramps)
Stage 4	Urticaria and a generalized anaphylactoid reaction; anaphylactic shock

remarkably occur. Cosmetic examples of agents to which also severe reactions have been reported are permanent hair dyes containing p-phenylenediamine, the sunscreen agents benzophenones, and hair bleaches (persulfates), which are often responsible for respiratory symptoms in hairdressers.[4,11,21] In a study that investigated the incidence and etiology of cutaneous reactions caused by cosmetics, 14 of 25 chemicals caused contact urticaria. Cinnamic alcohol, cinnamic aldehyde, eugenol, geraniol, anisyl alcohol, benzyl alcohol, coumarin, and balsam of Peru caused the most reactions. Comparing individuals with a history of cosmetic sensitivity to controls or those with eczematous skin, however, did not reveal a statistically significant increase in positive reactions. The high percentage of individuals including controls who reacted to these substances would indicate a non-immune mechanism.[20]

Dyes are widely used as colouring agents in cosmetics, foods, medications and textiles. They can cause a broad spectrum of clinical pictures including contact urticaria. Hair dyes, basic blue 99 dye, patent blue dyes, henna, red dyes, curcumin, and reactive dyes have all been reported as inducers of contact urticaria. It is likely that hair-dye constituents such as preservatives and intensifiers play an important role as contact urticaria causative agents.[16] Contact urticaria to nickel, simultaneous contact urticaria and a delayed-type contact allergy to thiocolchicoside, a case of severe contact urticaria with systemic involvement resembling an anaphylactic reaction following the application of a topical corticosteroid due to hexylene glycol, and a case of immunological contact urticaria caused by triclosan have also been reported.[22-25]

There is limited data about occupational immediate contact reactions. At an occupational dermatology clinic in Australia, the most common cause of work-related contact urticaria were shown as natural rubber latex (52%), followed by foodstuffs (35%) and ammonium persulfate. The patients included many chefs and some bakers, pastry cooks, and cooks.[5] In a French study, in a period of 2001–2010, natural rubber latex was the predominant cause (n=124) of occupational contact urticaria, although the number of that cases decreased significantly during the study period. Plants, grains and vegetables were the cause in only 15 cases.[6] In a Finnish study with a period of 12 years, occupations with the greatest frequency of contact urticaria/PCD involve bakers, cooks and chefs, farmers and farm laborers, veterinarians, gardeners, and hairdressers. The most common causative agents were cow dander and flour and grain, followed by natural rubber latex and other food. Within the food-related occupations, wheat and other flours were by far the most common cause of contact urticaria/PCD, with 76 cases, whereas fish and other animal-derived food caused 33 and other plant-derived food caused 23 cases. In 25 cases (4.4%), chemicals were the cause of contact urticaria. The compounds that caused contact urticaria most frequently were persulfates used in hair bleach products and carboxylic acid anhydrides used by the electronics sector as epoxy hardeners.[4] In another study which investigated the patients diagnosed with occupational contact urticaria or PCD, among 291 patients, 233 cases (80%) were diagnosed with contact urticaria and 59 cases (20%) with PCD during the study period. The majority (62%) of the patients were female. The most common causes were flour, grains and animal feed (21%), followed by cow dander (18%), natural rubber latex (15%), and chemicals (14%). Therefore, the patients with contact urticaria or PCD were most commonly food service workers (32%), farmers (21%), nurses (11%), and gardeners/florists (9%). Of the patients diagnosed with contact urticaria or PCD, 134 (46%) had a concomitant airway disorder caused by the same work-related agent.[26]

Food industry workers are known to be at risk of occupational contact urticaria caused by foods such as fruits, vegetables, seafood, and meat.[27,28] Foods known to cause ICU include fish, shrimp, meat, eggs, spices, milk, oats, and tree nuts as well as peanuts. Foods associated with NICU cause direct mast cell activation and release of histamine, such as alcohol, strawberries and tomatoes, and foods that contain histamine, such as matured cheeses, pickled herring, pineapple, red wine, sauerkraut, contaminated tuna, and yeast.[13] Vega et al. showed a series of 30 patients with occupational immunoglobulin E-mediated contact urticaria from *Thaumetopoea pityocampa* which is pine processionary caterpillar (nocturnal lepidoptera of the Thaumetopoeidae family). According to this study, pinecone or resin collectors, woodcutters, farmers and stockbreeders were the most frequently and seriously affected workers, probably as a result of dense exposure to the caterpillar.[29]

Natural rubber latex is the traditional material used in medical gloves, and is known to cause IgE-mediated immediate-type hypersensitivity.[30] While delayed hypersensitivity to latex has long been established, immediate hypersensitivity to latex is relatively recent, having been reported in literature for the first time in 1979.[31,32] Immediate type I hypersensitivity reactions to latex proteins, occur within few minutes after exposure to latex. Healthcare workers also constitute a high-risk group for the development of contact urticaria with natural rubber latex

being the most important allergen, although type 1 immediate hypersensitivity reactions is less frequent than irritant contact dermatitis and delayed-type hypersensitivity reactions.[30]

PROTEIN CONTACT DERMATITIS

This skin condition was described for the first time in 1976 by Hjorth and Roed-Petersen in food handlers which is distinctive from allergic contact dermatitis.[33] Proteins and proteinaceous materials are the cause and major allergens indicated by history and test results were fish and shell-fish in their case series.[33]

PATHOMECHANISM

The exact pathophysiological mechanism in PCD is yet unknown. Several authors have considered a combination of type I and IV allergic skin reactions to proteins, while this association has been difficult to prove in most cases.[13,33,34] Specific IgE seems to play an important role.[13]

CLINICAL PRESENTATION

The most frequent clinical presentation of PCD is a chronic or recurrent dermatitis. The lesions of PCD are usually restricted sharply to the site of protein contact. Clinical symptoms may occur 30 min after contact to the allergen.[13,34,35] It may appear as limited fingertip dermatitis which is often the first sign of eczematous dermatitis or spread to the wrists and arms. There may occasionally be an urticarial or vesicular aggravation a few minutes after contact with the triggering agent and the reaction may be accompanied by burning, stinging, pruritus or pain.[34,35] When the proximal nail fold becomes red and swollen after touching food or natural rubber latex, it was thought that these cases of chronic paronychia constituted a variety of PCD.[2,12,34] Individuals who react specific food proteins rarely exhibit systemic symptoms with oral ingestion.[17] When the causing allergen is avoided, PCD patients with recurrent chronic hand eczema may recover quickly. If there is a history of a immediate reaction to the allergen causing the dermatitis on the hands, a clinical diagnosis is made.[13]

Classically, the causative proteins are divided into 4 main groups;

Group 1: Fruits, vegetables, spices, plants, and woods

Group 2: Animal proteins

Group 3: Grains

Group 4: Enzymes

Considering the characteristics of the causative proteins, several occupations may be impacted.[34,35]

PCD is one of the more common occupational dermatoses and it affects the hands and forearms. The occurrence of PCD is mainly induced by occupational exposure to proteins in food professionals, farmers, animal breeders, veterinarians and healthcare professional.[13,36,37] Fishermen, cooks, and butchers are most commonly affected. Crustaceans and mollusks are more frequent triggers of food allergies than fish and can also be life threatening in individual cases.[37] But non-occupational cases can occur as well, for instance after handling protein-containing food for animals or fishing maggots.[13]

In a French study that investigated the characteristics and prevalence of PCD, 22 cases had occupational PCD, and 3 cases had non-occupational PCD. Among 22 cases of occupational PCD, 12 occurred in cooks sensitised to fish (5 cases), shellfish (2 cases), meat (2 cases), nuts (2 cases) and, in 1 patient for each of the following ingredients: egg, reblochon cheese, buckwheat, potato and alliaceae (garlic and onion). The 4 other cases of occupational PCD were due to amniotic fluid in a veterinarian, hydrolyzed proteins in a hair mask in a hairdresser, some flowers in a florist and to latex in a nursery. Of their patients, 68% of the 25 patients with PCD and 15/22 (68%) with occupational PCD had a history of atopy.[38]

As a result, PCD appears to be developing in individuals who are often and repeatedly exposed to protein, and it also occurs in patients who have a history of atopy. Microtrauma to the skin may promote the formation of PCD by allowing large proteins to penetrate through the skin. IgE-mediated immediate sensitization to proteins may result from such skin exposure, as demonstrated by prick tests or by the presence of circulating protein-specific IgE.[38]

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Clinical and Histopathological Features of Irritant Contact Dermatitis

İrritan Kontakt Dermatitin Klinik ve Histopatolojik Özellikleri

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ABSTRACT Irritant Contact Dermatitis (ICD) is the most common type of contact dermatitis and occupational dermatosis. ICD accounts 80% of all contact dermatitis. It is a multifactorial disease. Properties of the irritant, environmental and host related factors, exposure related parameters determine the clinical presentation. Although lesions may develop anywhere on the body, hands are one of the most affected areas during occupational or routine household activities. Clinical types of the disease mainly occur in a spectrum including subjective reactions, irritant reactions, acute ICD, acute delayed ICD, chronic ICD, chemical burn, traumatic ICD, pustular and acne-like ICD, frictional dermatitis, asteatotic ICD. Other clinical presentations such as airborne ICD, diaper dermatitis or Paederus dermatitis may also be seen. ICD may present with acute or chronic features. Histopathological features differ according to whether they are acute or chronic. In this section, clinical and histopathological findings of ICD are discussed.

Keywords: Contact dermatitis; irritant dermatitis; histopathology

ÖZET İrritan Kontakt Dermatit (İKD), kontakt dermatitlerin ve mesleki dermatozların en sık görülen tipidir. İKD, tüm kontakt dermatitlerin %80'ini oluşturur. Multifaktöriyel bir hastalıktır. İrritan etkenin özellikleri, çevresel ve konak ile ilişkili faktörler, maruziyetle ilgili parametreler klinik tabloyu belirler. Lezyonlar vücudun herhangi bir yerinde gelişebilse de, eller mesleki veya rutin ev aktiviteleri sırasında en çok etkilenen bölgelerden biridir. Hastalığın klinik tipleri esas olarak subjektif reaksiyonlar, irritan reaksiyonlar, akut İKD, akut gecikmiş İKD, kronik İKD, kimyasal yanık, travmatik İKD, püstüler ve akne benzeri İKD, friksiyon dermatiti, asteatotik İKD gibi bir spektrumda ortaya çıkar. Hava yoluyla gelişen İKD, bebek bezi dermatiti, Paederus dermatiti gibi diğer klinik prezentasyonlar da görülebilir. İKD akut veya kronik özelliklerle seyredebilir. Histopatolojik özellikler akut ya da kronik olmasına göre farklılık gösterir. Bu bölümde İKD'nin klinik ve histopatolojik bulguları tartışılmıştır.

Anahtar Kelimeler: Kontakt dermatit; irritan dermatit; histopatoloji

Irritant contact dermatitis (ICD) is the most common type of contact dermatitis, accounting for 80% of all contact dermatitis. It is also the most common occupational disease.[1-3] The frequent involvement site is the hands. ICD is a multifactorial disease which is mainly driven by innate immunity without an adaptive immune response. It is induced by physical factors (heat, cold, low humidity, sweating, UV radiation), mechanical factors (occlusion, friction, pressure, and vibration) and irritant agents. Single exposure to a strong acid, alkaline, oxidant or repeated exposure to irritants such as soaps, detergents, hand sanitisers, plants, water are the main causes of ICD.[1-4] Occupational involvement is frequently seen in wet workers such as cleaners, butchers, cooks, metal workers and health workers.[1] Chemical properties of the exogen material, the concentration, duration and amount of the irritant, the way of the exposure, environmental factors as humidity and intrinsic factors such as age, presence of atopy or other epider-

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mal barrier problems, repeated traumas (hand scrubbing, washing.. etc.), previous history of dermatitis affects the clinical presentation.[1-4]

Clinical types of the disease occur in a spectrum including subjective reactions usually without any lesions to an exaggerated reaction such as chemical burn. The clinical types of ICD are subjective reaction, irritant reaction, acute ICD, acute delayed ICD, chronic ICD, chemical burn, traumatic ICD, pustular and acne-like dermatitis, frictional dermatitis, and the other presentations of ICD.[1-2,5,6]

CLINICAL FEATURES

The anamnesis including the history of contact with the irritant, occupational conditions, the involvement site together with the clinical features help to make the diagnosis. Lesions may develop anywhere on the body according to the contact site of the irritant. But the body areas which face the irritants at first such as hands, face, neck, scalp are commonly affected. Of them, hand is the most frequent involvement site usually manifesting on the dominant hand. The irritant contact reaction may present with acute or chronic features.[1,2] Erythema with sharp margins, edema, vesicles, blisters in acute forms, erythema with dryness on the finger webs, tips, palms, and/or dorsum of the hands with sharp margins in irritant reactions and dryness, scales, lichenification and fissures in chronic types are observed. Fissures are the result of decreased elasticity and increased keratosis. Distant spread is not expected, and the disease is usually limited to the contact site.[4-8]

SUBJECTIVE/SENSORIAL IRRITATION

It is the problem of sensitive skin with stinging, tingling, sensation of burning and itching caused by contact of certain substances mainly cosmetics without any skin lesions. Sometimes physical or thermal stimuli may also cause these complaints. Cosmetic intolerance syndrome, which is described by Maibach is another type of subjective reaction. This type of reaction is common in women, rosacea patients or atopic patients. Environmental changes such as windy air, wet humid air, stress, or emotional changes may trigger the flares in some of these patients.[9-11] Sodium lauryl sulphate (SLS) which is commonly used in shampoos and cleansers is a frequent factor for these kinds of reactions. Beside SLS, retinoids, hydroxy acids, propylene glycol, lactic acid, azelaic acids, benzoic acid, benzoyl peroxide are the responsible agents.[1]

IRRITANT REACTION

An irritant reaction is a subclinical, mild form of irritant dermatitis with xerosis, scaling, mild redness, and edema (Figure 1). The reaction usually starts on fingers under occlusive rings or on the dorsal sides of the hands and may spread through the hand and forearm (Figure 2). By progression, vesicles, blisters, pustules, and erosions may develop. Perifollicular red spots around the follicles with pruritus are observed.[1,2] Scalp is also one of the most affected areas.[12] Low



FIGURE 1: Irritant reaction wild mild erythema with sharp margins, edema and pityriasiform scales.



FIGURE 2: Irritant reaction with erythema, xerosis and scratching on the dorsum of the hand.

potent irritant during repeated daily activities like washing hands with soap or washing the dishes with detergents without a protective glove or washing hair with shampoo including SLS, contact with the juice of some vegetables or fruits may cause this mild irritant reaction by disrupting epidermal barrier. Individuals exposed these factors such as hairdressers, housewives, cleaners develop this pre-eczematous condition. If this repeated irritant contact is discontinued, irritant reaction may resolve spontaneously. However, it may progress to a prominent eczematous reaction "chronic cumulative ICD" if the contact with the irritant persists, and the damage of the skin exceeds the repair capacity of the skin.[3-8]

ACUTE IRRITANT CONTACT DERMATITIS

Potent irritants such as strong acids, strong alkalis cause skin damage usually by direct contact. Therefore, acute ICD may develop due to occupational accidents.[1,3,13] It develops quickly within minutes to hours on the contact site and then begins to heal, which is described as "decrescendo phenomenon". On the other hand, allergic CD may worsen despite the removal of the agent, which is described as "crescendo phenomenon".[14] The symptoms start with stinging, burning, or pain. In the early stages of acute ICD, bright, well demarcated, erythema and swelling are observed. According to the degree of the reaction swelling may be associated with oozing, vesicles, blisters or necrosis (Figure 3). Acute irritant reaction may regress after removal of the contact. However, in some cases, the reaction may prolong.[3,5,6,8,14]

ACUTE DELAYED IRRITANT CONTACT DERMATITIS

Acute delayed ICD develops after 8-24 hours following the contact. Therefore, it may mimic allergic contact dermatitis. This reaction may be observed during patch testing and may cause a confusion if the reaction is irritant or allergic. Diffuse erythema with desquamation, dryness, edema, vesicles, blisters may be observed. The common irritants that cause acute delayed ICD are dithranol (anthralin), benzalkonium chloride, tretinoin, tetra ethylene glycol diacrylate, ethylene oxide, epichlorohydrin, podophyllin, propane sulphone, 2,4-Dichloro-5-Methylpyrimidine, chlorothalonil 0.01%, calcipotriol.[1,3,5,6,15]



FIGURE 3: Sharply demarcated erythema, together with vesicles, bullae and crusting due to contact of an acidic compound on the dorsum of the hand.

CHRONIC IRRITANT CONTACT DERMATITIS

Chronic ICD (CICD) also named "cumulative irritant contact dermatitis" is the eczema lasting more than 6 weeks. It is the most common form of ICD.[3] Chronic ICD is usually caused by the cumulative effect of the multiple weak irritants or repeated exposure to irritants in small concentrations such as soap, detergents, hand sanitisers, solvents, water, glue, paint, dust, plants, juice of fruits and vegetables, insecticide, cement, limestone, wood preservative, formalin, bleach.[2,7] Some fruits such as papaya and pineapple may also directly cause primary ICD because of their proteolytic enzymes.[16] When the irritants' cumulative damage exceeds the restoration capacity of epidermis, irritant reaction begins. If the contact with the irritant continue CICD develops. While irritant reaction resolves after the elimination of the irritant, CICD do not, because of the irreversible cumulative effect of the irritants. Atopic dermatitis may also manifest itself as CICD on the hands in adulthood.[1-8]

CICD may present as an occupational disease especially on the hands of health care workers, cleaners, hairdressers, metal workers, kitchen workers.[1-8] Interdigital web space involvement is frequent in CICD and sometimes the initial finding. Remnants of irritants on the webspace or under the ring, occlusive effect of adjacent fingers and having a thinner epidermis on the interdigital space result in an increased risk of development of ICD on interdigital areas. It should be also a warning for CICD. Besides that, the presence of interdigital ICD is an important risk factor for the development of sensitization to antigen.[17] Clinical findings of CICD include hyperkeratosis, lichenification, fissures and xerosis on an erythematous base. The borders are not sharply defined. Pruritus may associate with pain due to fissures (Figure 4).[5-8] Fingertip involvement is also frequent.[4] Fingertip eczema or pulpitis sicca is a typical presentation of CICD with erythema, xerosis with hyperkeratosis, fissures on the fingertips (Figure 5). Vesicles may associate and and pruritus is frequent. This involvement may also affect nails.[4]

CHEMICAL BURNS

This is an acute and severe form of ICD. Strong acidic substances or strong alkalis lead bright erythema, edema, pain within minutes to hours on the contact area. Phenols, weak hydrofluoric acid, and sulphur mustard gas can cause a delayed reaction several hours or a day after.[1,3,5,6] Immediate erythema is usually followed by blisters, erosions and even necrosis depending on the exposure way and duration. Hands, face, and neck are the most common locations of chemical burns. Beside skin, oropharynx, eyes, nose, epiglottis, liver, and other organs can also be affected. Alkaline burns effects deep tissues. Because alkalis cause barrier lipid denaturation. Deep tissues are protected better in acid burns than alkali burns because of the denaturation of the skin proteins resulting in eschar formation. Eschar colour may change according to the acid. Nitric acid causes yellow eschar, sulfuric acid causes black to brown colour, hydrochloric acid causes grey or white colour. Toxic chemicals may cause systemic side effects.[2,5,6]



FIGURE 4: Bilateral irritant contact dermatitis of the palms secondary to repeated contact with the solvents.



FIGURE 5: Mild erythema, hyperkeratosis with nail changes on the fingertips.

TRAUMATIC IRRITANT CONTACT DERMATITIS

Following an acute skin trauma such as chemical burn, fire burn, laceration; exposure to irritants, just before the healing completed, cause this type of dermatitis. It shows chronicity and may be recalcitrant to treatments. Nummular eczema like presentation on hands may be observed. Similar clinical findings with CICD such as erythema, scales, hyperkeratosis, fissures are observed. Nail involvement may also be seen.[5,6]

PUSTULAR AND ACNEIFORM IRRITANT CONTACT DERMATITIS

Metals, croton oil, mineral oils, tars, greases, asphalt, cutting oils, metalworking fluids, naphthalene, chlorinated aromatic hydrocarbons, fluorinated compounds usually by occupational exposure cause folliculitis and acneiform lesions on the exposure sites.[1,5,6] Among them chlorinated aromatic hydrocarbons (chlorinated dioxins) is the most potent acnegenic agents and most of them are also hepatoxic. The pustules are usually "sterile" and transient. Besides them, miliarial reactions with non-follicular pustular reaction, due to occlusive wearing, UV and infrared radiation can be seen particularly in patients with atopic dermatitis, seborrheic dermatitis, or prior acne vulgaris patients.[1,5]

FRICTIONAL DERMATITIS

Frictional dermatitis usually develops due to irritant effect of repeated trauma on daily activities or occupational conditions. Erythema, scales, fissures, and itch together with hyperpigmentation may be observed on the friction site.[1,5,18] It is characterized by hyperkeratosis, acanthosis, and lichenifcation.[18,19] There are some typical presentations of frictional dermatitis; intertrigo in all ages, "Pool Palms" and "Frictional Lichenoid Dermatitis" usually in childhood.

- **Intertrigo;** is the ICD on the flexural areas such as medial buttocks, vulva, axilla, intermammarian and perianal area caused by the friction of the skin folds to adjacent skin together with the retention of sweat and occlusion. Predisposing factors include obesity, hyperhidrosis, occlusive dressing, synthetic clothing, poor hygiene.[3,5,19]
- **Pool palms;** usually develop on palms and soles of children who have prolonged contact with the rough surface of the pool walls in summertime. Erythema together with vesiculation and pustules may be seen on the pressure sites such as fingertips.[20]

- **Frictional lichenoid dermatitis;** is another childhood presentation of frictional dermatitis.[19] It is frequent in summertime. Clinical features include pruritic, lichenoid papules on the elbows and the knees. It is supposed to be associated with the friction during outdoor activities such as playing on the playground, sandbox, or seaside. Role of UV is not clear. Histologic changes reveal nonspecific features, hyperkeratosis, acanthosis, lymphocytic infiltrate.[21,22.]

ASTEATOTIC IRRITANT CONTACT DERMATITIS

It is an eczematous change due to xerosis in elder and atopic individuals. It worsens in winter months because of cold, low humidity, however increased UV radiation also has a negative impact on this process. Bathing with irritants and neglecting to use moisturizers is a frequent reason in elderly individuals. Clinically, cracked, ichthyosiform polygonal scales with patchy eczematous appearance are observed usually on anterior lower legs. (Figure 6) Pruritus with burning is the main complaint. It can be observed as an occupational disease also.[1,5,6]

OTHER CLINICAL PRESENTATION OF IRRITANT CONTACT DERMATITIS:

NONERYTHEMATOUS OR SUBERYTHEMATOUS IRRITANT CONTACT DERMATITIS

It is usually detected during the measurement to check or screen the irritant effects of new cosmetics, chemicals, and textiles. In these reaction, epidermal alterations without visible inflammation which are usually detected by cutaneous bioengineering techniques such as squamometry, corneosurfametry are observed. There is no patient's complaint but there is the early sign of skin irritation without any clinical findings.[5,6]



FIGURE 6: Asteatotic ICD presenting with polygonal scales due to xerosis on the ankle.

AIRBORNE IRRITANT CONTACT DERMATITIS

Irritant substances are disseminated through the air and reach the skin by air transport. Limestone dust, metal dust, thyme dust, some steam or fumes, solvents, spice dust and perfume and deodorant sprays may trigger airborne ICD on uncovered sites such as face and V of the neck, arms and legs. Usually, it starts with a burning sensation and itch. Erythema, edema sometimes with blisters and scaling may be seen. On the face, eyelid edema and erythema with scaling, dryness are frequent findings. Sometimes conjunctivitis, nasopharyngitis with sore throat may accompany skin involvement. The clinic findings may mimic photoallergic or phototoxic contact dermatitis. Fiberglass may cause maculopapular lesions. Gas and spray form of some irritants may pass through the clothes and may accumulate on the flexural sites and by sweat and occlusion trigger ICD.[5,6,15,16,23-25]

PHOTOCONTACT IRRITANT DERMATITIS

Photoreactive chemicals are activated ultraviolet light (most often UVA spectrum) leads production of reactive oxygen species (ROS). The ROS cause damage of DNA, RNA and proteins.[26] Photocontact irritant dermatitis may be observed as berloque dermatitis and phytophotodermatitis. Phytophotodermatitis is associated with plants or plant derivatives, Umbelliferae species (e.g., celery, carrot) and Rutaceae species (e.g., lime, lemon, bergamot). Berloque dermatitis is a kind of fragrance dermatitis with hyperpigmented macules due to a photoactive compound bergapten. Bergapten is an ingredient found in bergamot oil. Other agents commonly inducing photo-irritant contact dermatitis are furocoumarins; 8-methoxypsoralen 4,5,8-trimethylpsoralen 5-methoxypsoralen, tar-related products such as coal tar, dyes such as methylene blue, eosin, disperse blue, amino-benzoic acid derivatives, amyl-ortho-dimethylaminobenzoic acid, fragrance materials and some plants: Lime, lemon, bergamot, burning bush, bitter orange, gas plant, parsnip, cow parsnip, wild chervil, Cruciferae, fennel, mustard, dill, common rue, celery, buttercup …etc.[26-28] The coal tar products developed the reaction in minutes while furocoumarins cause a delay reaction presenting 24-48 hours later. Airborne contact of these photo irritants may also cause a reaction on the sun exposed areas.[5,6]

IRRITANT CONTACT CHEILITIS (DRY, CRACKED LIPS)

The disease is caused by exogenous factors such as cold windy air, arid climates, sunburn, chronic licking of the lips, repeated trauma, picking up scales due to anxiety, chronic mouth breathing, irritant foods (such as citrus fruits, fruit juices, tomato, garlic, onion, fish, fermented cheeses) or endogenous factors such as atopia.[16,29,30] Chronic irritant cheilitis may be a part of atopic dermatitis because of chronic dryness in severe forms. Excess salivation, SLS in toothpaste, some chewing gums may also affect the barrier of the lips, predispose cheilitis. Some medications retinoids, antiemetics or chemotherapy may trigger cheilitis. Dryness, scales, erythema, and/or fissuring of the lips are the main clinical findings (Figure 7). Hyperpigmentation of the perioral area may accompany.[16,30]

IRRITANT PERIANAL CONTACT DERMATITIS

Irritants may cause perianal dermatitis. ICD on perianal area constitutes approximately 18% of the cases of perianal dermatitis.[31] The major irritants on this site may be the ingested irritant foods such as spices, tomatoes, citrus, caffeine, chocolate, tobacco. Deposition of the irritants such as faecal debris due the occlusive effect may also trigger ICD. The other frequent irritants are hygiene products, shaving, alcohol. The itch-scratch cycle leads chronic course which is usually presented with thickening of the anal folds, concentric superficial radial fissuring.[16,31,32]

IRRITANT SCALP DERMATITIS

ICD of the scalp is a frequent problem which is usually caused by hair cosmetics or trauma. The clinical presentation may change from subclinical subjective reaction to irritant reaction and chronic ICD. Trauma to the scalp ranges from massage, scratching, excoriations, friction to trichotillomania. SLS in hair cosmetics, irritant of hair dyes, hair conditioners, some medications such as calcipotriol, propylene glycol may cause irritation. Irritation may lead stinging, pruritus and painful sensation with contact. In the early stages, perifollicular erythema may be observed; by the progression, erythema, edema, folliculitis, scales and lichenification especially on the occipital and nape area may be observed. Chronic irritant dermatitis of the scalp may also trigger telogen effluvium.[12,33,34]



FIGURE 7: Scales and mild fissures on the lower and angular area of the lip.

IRRITANT DERMATITIS OF THE NAIL UNIT

Common nail irritants are nail cosmetics (nail enamel, nail enamel removers, methacrylic acid for sculptured nails, cuticle removers), detergents, soap, juices of vegetable and fruits, occupational chemicals, inappropriate glove wear causing maceration. Chronic ICD on the skin adjacent to the nail unit also cause nail alterations. Clinical findings include longitudinal ridging, paronychia, onychodystrophy, Beau lines, onycholysis, onychomadesis, koilonychia. Nail changes may be complicated by secondary infections with *Candida, Staphylococcus, Pseudomonas* and *Dermatophytes*.[16,35-38]

PAEDERUS DERMATITIS

It is a specific form of acute irritant contact dermatitis due to toxin of genus Paederus which is named as "Paederin". It causes sudden onset of erythema, vesicles, blisters together with pain, itch and usually burning sensation on the exposed area. Thus, named as "night burn" in Turkey.[39] At first, small vesicles appear 24-48 after the toxin contact and then turn into pustules or vesicles. The acute onset of the eruption in a linear pattern sometimes with kissing lesions on the flexural areas or showing uniaxial symmetry reminding also a mirror image, history of contact with the Paederus beetle are the clues for the diagnosis. The linear pattern of lesions due to toxin spurt from the insect's sac has also been defined as "railroad pattern".[40-42] Histopathology reveals no specific sign. In early lesions, histopathologic features of innate immune response with neutrophilic infiltration and spongiosis together with epidermal necrosis in some areas are observed. Perivascular edema in the dermis with a mixed interstitial infiltration may be seen in older lesions with acanthosis and parakeratosis in the epidermis, spared supra basal cells, scattered acantholytic cells.[42]

DIAPER DERMATITIS

It is a specific type of ICD on the perineal and perianal areas. Occlusion of sweat, water, urine, faeces on the diaper area in newborns, infants, and diapered elder individ-

uals due to urinary and/or faecal incontinence cause ICD. Faeces, urine together with the bacterial enzymes potentiate irritation. Clinical findings at early stage include erythema, edema on the convex surfaces and at the diaper margins with sharp borders together with the spared skin folds. By the progression superficial erosions may be observed and Candidiasis infection by C. albicans, a normal flora agent, may superposed this condition presenting with erythema, desquamation, and satellite papules/pustules. In elder, pressure ulcers may develop.[1-5]

PSEUDOFOLLICULITIS

It is a chronic condition which is triggered due to shaving, hair removal or ingrown hairs together with an inflammation of follicular and perifollicular skin. Beard area is mostly involved which is named as "Pseudofolliculitis barbae". The other areas with terminal hairs may also be affected. African and Asian men and hirsute women who have curly hair are more frequently affected.[43] The clinical findings are erythematous papules, pustules with ingrown hairs in the center which may also be seen clearly with dermoscopy. Post-inflammatory hyperpigmentation may associate because of repeated trauma. Friction or long-term water contact is reported to cause irritant aseptic folliculitis in athletes, fisherman.[44]

PIGMENT CHANGES DUE TO IRRITATION

Hyperpigmentation due to heavy metals or ***hypopigmentation*** (contact vitiligo, chemical leucoderma) due to phenolic chemicals have been reported.[3,45] Repeated exposure to some chemicals mainly such as aromatic or aliphatic derivatives of phenols and catechols may damage melanocytes.[45] Occupational exposures to some chemicals such as para-tertiary butyl phenol (PTBP) and para-tertiary octyl phenol (PTOP), para-tertiary butyl phenol formaldehyde (PTBPF), para-tertiary butyl catechol (PTBC), para-tertiary amyl phenol (PTAP) has been reported to cause depigmentation.[46]

HISTOPATHOLOGIC FEATURES:

Histopathology of ICD reveals nonspecific features. In the acute forms, spongiosis, exocytosis, intracellular vacuolation, neutrophil-rich superficial perivascular infiltrate plus widely scattered necrotic keratinocytes in the epidermis are observed.[5,47,48] Due to the potency of the irritant, epidermal necrosis or even loss of epidermis and subepidermal clefting may be observed. Besides it, different irritants may trigger different histopathologic features at the early stage. For example: SLS irritation predominate parakeratosis, detergents harm superficial stratum corneum, organic solvents damage epidermal or dermal structures, nicotinates cause vascular changes causing erythema, croton oil cause a pustular reaction.[14] By the ICD get chronicity, histopathologic findings share common features. Chronic ICD reveals acanthosis with mild hypergranulosis, hyperkeratosis, parakeratosis, lichenification, perivascular lymphohistiocytic infiltrate.[48]

CONCLUSION

ICD is a common problem in daily and occupational life. The main clinical types include acute ICD, delayed acute ICD, chronic ICD. Histopathologic features change according to these presentations without any specific features. Anamnesis is very important to understand the predisposing factors together with the clinical findings. Clinical findings vary due to the involvement site, irritant related factors, irritant's exposure way, its duration and frequency, host related factors, environmental, physical factors contribute to the presentation.

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Clinical and Histopathological Features of Allergic Contact Dermatitis

Alerjik Kontakt Dermatitin Klinik ve Histopatolojik Özellikleri

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ABSTRACT Allergic contact dermatitis (ACD) is an inflammatory disease of the skin that is caused by a type 4 hypersensitivity reaction. The most common clinical feature of acute ACD is eczematous dermatitis. In contrast to the classic picture, non-eczematous types of ACD such as erythema-multiforme-like, lichenoid, purpuric, bullous, pigmented, lymphomatoid, granulomatous or pustular ACD have also been reported. Histopathology of ACD shows lymphocytic perivascular infiltration, dense dermal edema, epidermal spongiosis and exocytosis in the dermis, while epidermal hyperplasia is more prominent in chronic lesions.

Keywords: Dermatitis, allergic contact; clinical features; histopathology

ÖZET Alerjik kontakt dermatit (AKD), tip 4 aşırı duyarlılık reaksiyonunun neden olduğu derinin inflamatuar bir hastalığıdır. Akut AKD'nin en sık görülen klinik görünümü ekzematöz dermatittir. Klasik görünümden farklı olarak eritema-multiforme benzeri, likenoid, purpurik, büllöz, pigmente, lenfomatoid, granülomatöz veya püstüler AKD gibi ekzematöz olmayan AKD tipleri da bildirilmiştir. AKD histopatolojisinde dermiste lenfositik perivasküler infiltrasyon, yoğun dermal ödem, epidermal spongioz ve ekzositoz görülürken, kronik lezyonlarda ise epidermal hiperplazi daha belirgindir.

Anahtar Kelimeler: Dermatit, alerjik kontakt; klinik özellikler; histopatoloji

Allergic contact dermatitis (ACD) is an inflammatory disease of the skin caused by a type 4 hypersensitivity reaction. This results from skin contact with a chemical or antigen and the subsequent T cell-mediated response. ACD accounts for 20% of contact dermatitis, and allergens vary greatly by geography, personal habits, hobbies, and types of preservatives.[1]

The most common clinical feature of acute ACD is eczematous dermatitis, but the clinical appearance may vary depending on its duration and location. Lesions are characterized by erythema, papules, confluent vesicles, or bullae, depending on the intensity of the allergic reaction. In severe reactions, this may lead to abundant oozing and the formation of yellowish crusts after a while. In mild cases, the only findings of allergic contact dermatitis consist of erythema and fine papules.[2]

In ACD, the rash usually begins 5-7 days after the first contact with the allergen. After repeated contact with the same (or chemically closely related) allergen, symptoms appear within 1-3 days. The symptoms subside within a few days after contact is discontinued. Regardless of the intensity of the reaction, the edges of the lesions are often undefined and extend beyond the area of contact with the allergen. This clinical appearance is the opposite of the sharply defined lesions seen in irritant contact dermatitis.[2]

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When ACD occurs in some anatomical regions, there may be different clinical appearances. For example, allergic contact dermatitis on the scalp is not only erythematous but also causes scaly. Edema is evident in the eyelids, scrotum, penis and earlobe. Allergic contact stomatitis or vulvitis is characterized by widespread erythematous and sometimes edematous plaques without vesiculation.[2]

In the subacute phase, the erythema subsides and small crusts and pityriasis scales form. If contact with the allergen continues, a chronic phase may occur with the development of lichenification, characterized by thickening and hardening of the skin and the prominence of normal skin creases.[3]

Chronic ACD has a monomorphic appearance in all cutaneous areas and is observed as thickened, scaly, and sometimes fissuring dermatitis with or without vesicles.[2]

Itching always accompanies allergic eczematous contact dermatitis and is often severe, but this finding is not specific to allergic contact dermatitis. However, in irritant contact dermatitis, burning and pain are more prominent. Although ACD can be localized anywhere on the body, the hands are the most common site.[2,3]

Histologic analysis of biopsy specimens of skin lesions in irritant CD and allergic CD often shows nonspecific presentations, including spongiosis, numerous neutrophils in the epidermis, swollen capillaries in the subepidermal dermis, and perivascular lymphocytic infiltrates.[4]

Histopathology of ACD shows lymphocytic perivascular infiltration, intense dermal edema, epidermal spongiosis and exocytosis in the dermis. Typically, in the very early stages of ACD, the histology of lesional skin is characterized by spongiosis, which is usually most prominent in the lower epidermis. Spongiotic vesicles may then form at various levels in the epidermis. Infiltration of lymphocytes, Langerhans cells, and macrophages is seen in the upper dermis around the superficial vessels. Eosinophils are frequently seen, but their absence does not exclude ACD. Eosinophilic exocytosis is common in ACD. When lesions persist in chronic allergic CD, hyperplasia (acanthosis, hyperkeratosis, parakeratosis) with a small amount of spongiosis and mixed dermal inflammatory infiltration is observed in the epidermis. Hypergranulosis is a feature frequently seen in rubbed lesions. Spongiosis and vesiculation are much less common in chronic lesions. [4,5]

Non-eczematous forms of ACD are also reported, such as erythema-multiforme-like, lichenoid, purpuric, bullous, pigmented, lymphomatoid, granulomatous, or pustular ACD.[3,6]

Apart from its typical clinical presentation, ACD can be seen as a regional dissemination. The best example of this clinical condition is erythema multiforme-like lesions. In this case, the clinical picture is characterized by typical targeted, urticarial and vesicular lesions as in erythema multiforme, but histopathology includes findings of spongiotic dermatitis. Early lesions are eczematous and localized at the allergen contact site. The erythema multiforme-like eruption occurs 1-15 days after the initial eczematous lesions and spreads around the original lesions or extends to the other cutaneous regions. It can be elicited by different substances, particularly exotic woods, medicaments, and ethylenediamine. In the histology, the epidermis shows spongiosis and exocytosis. There is mild edema and perivascular lymphohistiocytic infiltration in the upper dermis. Vacuolar degeneration of basal cells and epidermal necrosis are very mild or absent. If bullae occur, they are located intraepidermally. The diagnosis is mainly based on positive patch testing with the suspected allergen. The patch test reaction is usually of the eczematous type; rarely, it can be urticarial.[2,7]

Lichenoid ACD is rare, and it is a lichen planus-like or lichenoid adverse drug reaction-like type of ACD. The diagnosis is usually made by histologic examination showing mild dermal lichenoid band infiltration with epidermal spongiosis and eosinophilia. Allergic contact stomatitis due to mercury orthodontic amalgam is a classic example of this type and usually presents as erosive lichen planus on the mucosa adjacent to the dental restoration. P-phenylenediamine, chromates, cobalt, nickel, and palladium are the other allergens in this type of ACD.[2,3,6]

Purpuric ACD is characterized by petechial and purpuric lesions, observed on the lower limbs, especially the ankles. Histological examination shows spongiosis and lymphocytic exocytosis in the epidermis and signs of leukocytoclastic vasculitis in the upper dermis. Isopropyl-N-phenyl-p-phenylenediamine and mercaptobenzothiazole are the most commonly reported allergens. It can also be associated with sensitization to balsam of Peru, topical NSAIDs, and kinase inhibitors.[2,3,7]

Bullous ACD is characterized by localized blisters at the site of contact with the culprit allergen. Histopathological examination with direct immunofluorescence can be performed to exclude bullous pemphigoid or other cutaneous autoimmune bullous disorders. This noneczematous form is usually caused by sensitization to cinnamic aldehyde, cinnamyl alcohol, thimerosal, and bufexamac.[3]

Pigmented ACD presents with marked pigmentation during the acute phase of eczema, which is often long-last-

ing even after the resolution of the dermatitis. Azoic dyes, cosmetics and fragrances are the most commonly implicated agents in this type. Some dermatological conditions, such as Rielh's melanosis and Civatte's poikiloderma, are considered pigmented forms of ACD, both of which are associated with sensitizing fragrances. Histology evidenced melanin deposits in the upper dermis. In this form of ACD, a positive patch test may induce a hyperpigmented area after the eczematous reaction disappears.[2,3,6,7]

A lymphomatoid variant is an entity defined based only on histopathological criteria, not clinically. Clinical symptoms resembling mycosis fungoides are observed along with itchy erythematous edematous papules or plaques in the area where the contact allergen is applied. Histopathological examination reveals the presence of a significant dermal (and sometimes subdermal) infiltration showing features of pseudolymphoma. Spongiotic dermatitis, in which atypical lymphocytes are not found on histopathological examination, and patch testing allow differential diagnosis. Gold, nickel, cobalt, and kaolin are typically associated with this ACD subtype.[2,3,6]

The pustular type is usually associated with textile dyes such as disperse blue and disperse red. Pustular ACD presents an erythematous area with non-follicular sterile pustules localized at the site of contact with the allergen. Nitrofurazone, isoconazole, minoxidil and merbromin are other known contact agents. Differential diagnoses include acute generalized exanthematous pustulosis, subcorneal pustular dermatosis, palmoplantar pustulosis, and pustular psoriasis. Histology revealed perifollicular lymphocytes, histiocytes and eosinophils. Patch testing usually shows a pustular reaction.[3,6,7]

Granulomatous ACD presents clinically as bright papular or nodular lesions ranging in color from reddish to brown and develops 4-6 weeks after exposure to the culprit allergen following an initial vesicular eruption. The presence of sarcoid granulomas in histopathological examination makes the differential diagnosis of sarcoidosis almost impossible. Deodorants containing zirconium are the main cause of this type of ACD. Tattoo inks containing chromium, cobalt, and cadmium, vaccines containing aluminum hydroxide, pacemakers containing mercury, beryllium, gold, palladium and titanium are other causative agents.[3,6]

Consort ACD, also known as connubial contact dermatitis, occurs due to exposure to an allergen from a other person. Allergens implicated in consort ACD are commonly cosmetic products such as lipsticks, moisturizers and aftershave as well as topical medications.[8,9]

Other types of ACD are airborne contact dermatitis and photoallergic contact dermatitis. In airborne contact dermatitis, allergens are transported by air. In most cases, classic eczematous lesions are located on the face, neck and decollete. Photophobia and conjunctival erythema may be present. Unlike photoallergic contact dermatitis, there are no spared areas and lesions are also present behind the ear and under the chin. If the allergen is capable of passing under clothing, the lesions can also reach closed areas. The borders of eczematous lesions are not clear and there is no definitive clinical finding distinguishing irritant or allergic airborne contact dermatitis. The main allergens that cause it are occupational allergens, cosmetics and plants. Clinical manifestations usually resolve a few days after the elimination of exposure to the allergen.[2,3]

Photoallergic contact dermatitis is a type IV delayed-type cutaneous reaction induced by skin contact with a photo antigen in previously sensitized individuals and triggered by ultraviolet radiation. It affects skin areas exposed to the sun, and areas such as behind the ear and under the chin are usually spared compared to airborne contact dermatitis. Skin lesions usually appear within 24 hours of sun exposure and present as eczematous dermatitis which is very itchy and spreading rash. The most common photoantigens are topical products such as fragrances, antimicrobials, and nonsteroidal anti-inflammatory drugs.[3,8]

Systemic contact dermatitis is a less common subtype of ACD. It is defined as a widespread eczematous reaction occurring following systemic exposure (e.g. ingestion, inhalation, or parenteral administration) to an allergen previously associated with allergic contact dermatitis in the same individual. [6] If a systemic ACD reaction may also occur, it is elicited by drugs, especially antibiotics; This variant has been described as symmetrical drug-induced intertriginous and flexural exanthema and typically involves the buttocks.[8]

Other clinical manifestations of systemic ACD include vesicular hand dermatitis, vasculitis or erythema multiforme-like lesions, diffuse maculopapular lesions, eyelid edema or dermatitis, exacerbation at sites of previous patch test reaction, and worsening of underlying eczematous dermatitis.[8]

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Phototoxic and Photoallergic Contact Dermatitis

Fototoksik ve Fotoalerjik Kontakt Dermatitler

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ABSTRACT Here will be discussed photoirritant and photoallergic dermatitides caused by topical or systemic exogenous substances. Photoirritation may or not be depended on oxygen. In photoallergy, haptens may be the transformed or untransformed substances. The main culprits are plants, fragrances, sunscreens, and antimicrobial, anti-inflammatory, cardiovascular, psychotropic, and chemotherapeutic drugs. Photosensitive dermatitides may cause many appearances resembling sunburn, eczema, urticaria, lichen planus, porphyria, or lupus erythematosus. They may also present as dyspigmentation. A distribution involving exposed areas and sparing shaded areas is a clue for diagnosis of photodermatoses. Although photoirritant and photoallergic dermatitides may coexist, a clinican should know distinguishing features between them, e.g. early or late onset after exposure. A photosensitive dermatitis, should also be differentiated from idiopathic photodermatoses e.g., polymorphic light eruption. Photopatch and photoprovocation tests may be useful in determining the photoallergen. Elimination of photoreactive substances, photoprotection, and anti-inflammatory measures are the main arms of management of photosensitive dermatitides.

Keywords: Contact dermatitides, photoallergic; contact dermatitides, phototoxic; contact dermatitides, photosensitive

ÖZET Bu bölümde, topikal veya sistemik ekzojen maddelerin neden olduğu fotoirritan ve fotoalerjik dermatitler tartışılacaktır. Fotoirritan dermatit oluşumunda oksijen bağımlı veya oksijen bağımsız reaksiyonlar yer alır. Fotoalerjide haptenler dönüştürülmüş veya dönüştürülmemiş maddeler olabilir. Başlıca etkenler bitkiler, kokular, güneş kremleri, antimikrobiyal, anti-inflamatuar, kardiyovasküler, psikotropik ve kemoterapötik ilaçlardır. Fotosensitif dermatitler güneş yanığı, ekzema, ürtiker, liken planus, porfiri veya lupus eritematozusa benzeyen çeşitli klinik görünümlere neden olabildiği gibi yalnızca dispigmentasyon ile de ortaya çıkabilir. Lezyonların güneş gören bölgelerde görülüp, güneşten korunan bölgelerde görülmemesi, fotodermatozların tanısı için önemli bir ipucudur. Fotoirritan ve fotoalerjik dermatitler bir arada görülebilir. Ancak, bir klinisyen, karşılaşma sonrası erken veya geç başlangıç gibi, bu dermatitler arasındaki ayırt edici özellikleri bilmelidir. Fotosensitif dermatitler, polimorfik ışık erüpsiyonu gibi idiyopatik fotodermatozlardan da ayırt edilmelidir. Fotoyama ve fotoprovokasyon testleri fotoalerjenin belirlenmesinde faydalı olabilir. Fotoreaktif maddelerin ortadan kaldırılması, fotokorunma ve anti-inflamatuar yöntemler fotosensitif dermatitlerin yönetiminin temellerini oluşturur.

Anahtar Kelimeler: Kontakt dermatit, fotoalerjik; kontakt dermatit, fototoksik; kontakt dermatit, fotosensitif

Although the title of this chapter is “Photosensitive Contact Dermatitis”, it may be more useful to discuss photosensitive reactions to exogenous chemical substances reaching the skin either topically or systemically. A photoreactive chemical substance may cause a dermatitis either by its direct toxic effects or by inducing hypersensitivity reactions. So, the resultant dermatitis is called “photoirritant dermatitis” or “photoallergic dermatitis”, respectively. Taking into consideration also the ways in which culprit chemical substances reach the skin, photosensitive

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dermatitides may be divided into four types: topical photoirritant dermatitis, systemic photoirritant dermatitis, topical photoallergic dermatitis, and systemic photoallergic dermatitis.

MECHANISM

A photoreactive chemical substance, also known as chromophore, absorbs a photon, namely a massless packet of light energy.[1,2] So, the molecule goes into an excited state. When it returns to the ground state, the cell is affected by several ways: energy transfer, electron or hydrogen transfer, covalent binding, and decomposition. Energy is transferred to the oxygen. Electron or hydrogen transfer results in the formation of reactive oxygen species. Both of these events are known as oxygen-dependent or photodynamic reactions and lead to oxidative damage.

As for oxygen-independent or nonphotodynamic reactions, the first type is again electron or hydrogen transfer, so that the photoreactive chemical substance may interact with cell components. In the second type, the photoreactive chemical substance establishes covalent bonds with cellular macromolecules, so that stable photoproducts are formed. Binding of psoralen to DNA is an example of this type reaction. In the third type, the photoreactive chemical substance undergoes decomposition, so that the resultant photoproduct may react with cellular components or may act as a new photoreactive chemical substance. The mechanisms mentioned so far leads to photoirritant dermatitis, also known as phototoxic dermatitis.

As for photoallergic dermatitis, after the photoreactive chemical substance goes into an excited state, there are two ways leading to a photoallergen.[3] In the first way, the absorbed energy is used to transform the photoreactive chemical substance into a hapten. Then, the hapten is linked to a protein to form a photoallergen. In the second way, the absorbed energy is used to conjugate the photoreactive chemical substance itself to a protein by a covalent bond to form a photoallergen. The chemical substance of the first way is called prohapten; and that of the second way, photohapten.[4] After both ways, the photoallergen triggers mainly a type IV hypersensitivity.

PHOTOREACTIVE CHEMICAL SUBSTANCES

Photoreactive chemical substances are listed in Table 1.[2,5-10]

LIGHT SPECTRUM

Both photoirritant and photoallergic dermatitides are most commonly caused by UVA.[5,11] However, action spectrum is wide in the former, while narrow in the latter.[6] Not only UVA, but also UVB, visible light, and infrared light may also lead to photosensitive dermatitides.[7]

CLINICAL PRESENTATION

Simply, photoirritant dermatitis looks like an exaggerated sunburn; and photoallergic dermatitis, allergic contact dermatitis. However, other clinical presentations may also be seen in photosensitive dermatitides. Upon sun exposure, an immediate transient erythema with prickling and burning may develop in patients using benoxaprofen.[7] Although this drug has been removed from the market, a same reaction has also been observed due to other systemic drugs such as amiodarone and vemurafenib. Again, as an immediate reaction, urticaria may develop in patients using photodynamic therapy with 5-aminolevulinic acid or in subjects using some sunscreens containing octocrylene or oxybenzone.

A photosensitive -particularly a photoirritant- dermatitis may also mimic porphyria, pellagra, lichen planus, or lupus erythematosus.[7,8] Porphyria-like lesions has been reported to be due to celecoxib, ciprofloxacin, finasteride, furosemide, imatinib, metformin, nalidixic acid, naproxen, sunitinib, tetracyclines, torsemide, or voriconazole. Pellagra may be seen in the prolonged use of isoniazid. Pellagra-like lesions has been reported to be due to azathioprine, 5-fluorouracil, or 6-mercaptopurine.

A hypo- or hyperpigmentation may be the only presenting sign of a photosensitive dermatitis.[7] Flutamide and hydrochlorothiazide are systemic drug examples capable of causing residual vitiliginous lesions. As for hyperpigmentation, berloque dermatitis is a well-known example. It is caused by sunlight and perfumes containing especially oil of bergamot.[8] One of constituents of this oil is bergapten (5-methoxy-psoralen). In the acute phase, berloque dermatitis is clinically characterized by erythema at the site where the perfume is applied.[12] Blistering may also be seen. Later, a well-defined hyperpigmented patch develops. Because the perfume may flow out from the application site due to the gravity, linear bands may also occur extending out from this site.

Essentially, berloque dermatitis is an example for phytophotocontact dermatitis, also known as phytophotodermatitis.[8] If a photosensitive dermatitis occurs after a contact to a plant containing furocoumarins or to a product prepared from such a plant, these terms are used. Another example for phytophotodermatitis is meadow grass dermatitis. It is characterized by linearly arranged blisters

TABLE 1: Photoreactive chemical substances.[2,5-10]

Antibacterial
- cefotaxime
- ceftazidime
- ciprofloxacin
- clinafloxacin
- dapsone
- demeclocycline
- doxycycline
- enoxacin
- fleroxacin
- gatifloxacin
- gemifloxacin
- grepafloxacin
- isoniazid
- levofloxacin
- lomefloxacin
- lymecycline
- minocycline
- moxifloxacin
- nalidixic acid
- norfloxacin
- ofloxacin
- pefloxacin
- pyrazinamide
- sparfloxacin
- sulfamethoxazole
- sulfanilamide
- tetracycline
- trimethoprim
- trovafloxacin
- ulifloxacin

Antifungal
- buclosamide
- dichlorophene
- griseofulvin
- itraconazole
- Jadit
- ketoconazole
- Multifungin
- omadine
- terbinafine
- thiobischlorophenol
- voriconazole

Antiviral
- acyclovir
- amantadine
- efavirenz
- simeprevir
- tenofovir

Antiseptic
- bithionol
- chlorhexidine
- dibromsalan
- hexachlorophene
- Impregon
- tribromsalan
- trichlorocarbanilide
- triclosan

Cardiovascular
- amiodarone
- amlodipine
- bumetanide
- candesartan
- captopril
- chlorthalidone
- clopidogrel
- diltiazem
- dronedarone
- enalapril
- fenofibrate
- furosemide
- hydrochlorothiazide
- indapamide
- irbesartan
- losartan
- methyldopa
- meticrane
- nifedipine
- olmesartan
- quinapril
- quinidine
- ramipril
- rilmenidine
- simvastatin
- telmisartan
- tilisolol
- torsemide
- triamterene
- triflusal
- valsartan

Chemotherapeutic
- azacitidine
- azathioprine
- bicalutamide
- brigatinib
- capecitabine
- crizotinib
- dabrafenib
- dacarbazine
- doxorubicin
- epirubicin
- erlotinib
- fluorouracil
- flutamide
- hydroxyurea
- imatinib
- mercaptopurine
- methotrexate
- mogamulizumab
- paclitaxel
- pazopanib
- rovalpituzumab
- sunitinib
- tegafur
- vandetanib
- vemurafenib
- vinblastine

NSAID
- aceclofenac
- ampiroxicam
- aspirin
- azapropazone
- benoxaprofen
- benzydamine
- carprofen
- celecoxib
- diclofenac
- etofenamate
- flufenamic acid
- ibuprofen
- indomethacin
- ketoprofen
- meclofenamic acid
- nabumetone
- naproxen
- oxaprozin
- oxyphenbutazone
- phenylbutazone
- piketoprofen
- piroxicam
- sulindac
- suprofen
- tiaprofenic acid

Psychotropic
- alprazolam
- amitriptyline
- aripiprazole
- chlordiazepoxide
- chlorproethazine
- chlorpromazine
- citalopram
- clomipramine
- clozapine
- escitalopram
- fluoxetine
- flupentixol
- fluphenazine
- fluvoxamine
- haloperidol
- imipramine
- olanzapine
- paroxetine
- perazine
- perphenazine
- phenelzine
- prochlorperazine
- promethazine
- risperidone
- sertraline
- thioridazine
- trifluoperazine
- venlafaxine

Other systemic
- afloqualone
- atorvastatin
- carbamazepine
- cevimeline
- chloroquine
- clopidogrel
- diphenhydramine
- eculizumab
- esomeprazole
- ethinylestradiol
- etretinate
- fenofibrate
- finasteride
- glibenclamide
- glipizide
- hydroxychloroquine
- isotretinoin
- leflunomide
- Malarone
- mequitazine
- mesalazine
- mesna
- metformin
- pantoprazole
- pirfenidone
- pravastatin
- promethazine
- quinidine
- quinine
- ranitidine
- repirinast
- simvastatin
- sitagliptin
- sulfasalazine
- tocilizumab
- triflusal

Coal tar
- acridine
- anthracene
- phenanthrene

Dye
- anthraquinone
- eosin
- methylene blue
- p-phenylenediamine
- rose Bengal

Fragrance
- benzophenone
- ethoxycoumarin
- methoxycoumarin
- methylcoumarin
- musk ambrette
- musk xylene

Plant
- angelica
- bergamot
- bishop's weed
- carrot
- celery
- coast spice bush
- common rue
- cow parsley
- cow parsnip
- fennel
- fig
- garlic
- gas plant
- giant hogweed
- lemon
- lime
- milfoil
- mokihana
- orange
- parsley
- parsnip
- ragweed pollen
- rue
- Saint John's wort
- stinking mayweed

Sunscreen
- AakoSun OMC
- Amiloxate
- avobenzone
- cinnamates
- dibenzoylmethane
- ecamsule
- Ensulizole
- enzacamene
- ethylhexyl salicylate
- hexenyl salicylate
- homosalate
- mexenone
- octisalate
- octocrylene
- octyl triazone
- octinoxate
- oxybenzone
- PABA
- Padimate-O
- Parsol
- sulisobenzone

Other topical
- 5-ALA
- benzocaine
- cadmium sulfide
- chromate
- cobalt
- Daconil
- Dangard
- dibucaine
- dictamnin
- fenitrothion
- hydrocortisone
- maneb
- methoxypsoralen
- porfimer sodium
- pyridoxine
- quindoxin

NSAID: Nonsteroidal antiinflamatuar drug

sometimes forming a crisscross pattern 12 to 24 hours after exposure to wild parsnip. The blisters heal in a short time leaving a long-lasting hyperpigmentation.

Another a well-known example for phytophotodermatitis is *dermatitis ficus carica*. This dermatitis is caused by fig leaf sap, also known as fig latex or fig milk.[13] Clinically, it resembles meadow grass dermatitis. In our country, this phytophotodermatitis is seen in subjects who collect raw figs to make jam.

EXPOSED AND SHADED AREA

Not only photosensitive dermatitides but also other photosensitive dermatoses prefer to involve some skin regions, namely exposed areas, and spare some other skin regions, namely shaded areas.[8,14] The most commonly exposed areas are the face, neck, "V" area of the chest, dorsal hands, and extensor and radial forearms. The dorsal feet and legs follow them. The main shaded areas are the scalp, other densely hairy areas, folds of the upper eyelids, retroauricular areas, subnasal area, and submental area. The antecubital fossae and finger webs are also rarely involved. A sharp cut-off line located under the cuff of a sleeve is a clue for photosensitive dermatoses. Similarly, areas under accessories such as rings and watches and areas under straps of garments such as sandals are usually spared. If a sufferer has been exposed to sunlight during a car drive, the exposed side of both the face and forearms are affected more severely, so that an asymmetrical, even a unilateral distribution develops.

Airborne contact dermatitides may also show a distribution similar to that of photosensitive dermatoses.[8] However, they usually involve the main shaded areas for photosensitive dermatoses.

PHOTOIRRADIATION *VERSUS* PHOTOALLERGY

Although a division between photoirritant and photoallergic dermatitides is not a superfluous effort, both mechanisms, namely photoirritant and photoallergic reactions, often coexist.[7] Furthermore, a photoirritant dermatitis favors sensitization to the photoreactive chemical substance. Nevertheless, it is useful to know clinical differences between photoirritant and photoallergic dermatitides, particularly in acute cases. Table 2 summarizes such differences.[6-8,11]

TABLE 2: Clinical differences between photoirritant and photoallergic dermatitides.[6-8,11]

Feature	Photoirritant	Photoallergic
Reaction on first exposure	Yes	No
Latent period after first exposure	No	Yes
Reaction time	Minutes to hours	Hours to days
Dose of photoreactive chemical substance	High	Low
Cross reactions to structurally related agents	No	Yes
Sharp borders	Yes	No
Tendency to spread	No	Yes
Covered areas	Not involved	Possibly involved
Resolution	Quick	Slow
Residual pigmentation	Yes	No
Persistent light reaction	No	Yes

DIFFERENTIAL DIAGNOSIS

Photosensitive dermatitides may mimic both other eczematous dermatoses and other photosensitive dermatoses. Photosensitive distribution of lesions is usually helpful in differentiating photosensitive dermatitides from other eczematous dermatoses. However, photosensitive atopic dermatitis is an exception. Most patients with atopic dermatitis benefit from ultraviolet therapy.[15] A small proportion of them worsen during this therapy. This is an example of photosensitive atopic dermatitis. This form is characterized by a photodistributed rash. However, typical atopic dermatitis lesions are also seen in covered areas.

As for other photosensitive dermatoses, it is not common that a photosensitive dermatitis mimics porphyria, pellagra, or lupus erythematosus. Even so, the best approach for differentiating photosensitive dermatitides from these diseases is that each patient with a possible diagnosis of one of them should be meticulously evaluated for exposure to chemical substances capable of causing them.

Some photodermatoses are gathered under the heading of "idiopathic" or "immune-mediated" photodermatoses.[5,16] They are polymorphic light eruption, solar urticaria, hydroa vacciniforme, actinic prurigo, and chronic actinic dermatitis. Polymorphic light eruption, as its name suggests, may cause various lesions such as papules, plaques, vesicles, and eczema. However, the last one is rare. On the other hand, some patients with polymorphic light eruption claim that sunscreens, one of the most common causes of photoallergic contact dermatitis,[8] exacerbate their eruptions. Such a claim arouses suspicion of photoallergy to the sunscreen. It is also possible that the sunscreen filters UVB effectively, but not UVA, so UVA induces polymorphic light eruption.[17]

Since photosensitive dermatitides may present as urticarial lesions, patients with solar urticaria should be interrogated about use of chemical substances capable of causing photocontact urticaria. Hydroa vacciniforme can easily be distinguished, since it heals with varioliform scars. Actinic prurigo predominantly affects American Indian children. Although its papules coalesce into lichenified plaques so that they give an eczematous appearance, patients also suffer from conjunctivitis and photophobia. These eye complaints are not usual in photosensitive dermatitides. Chronic actinic dermatitis is characterized by chronic persistent, often lichenified eczema on exposed areas. However, later in its course, the disease may extend to covered areas and even may progress to erythroderma.[17] Chronic actinic dermatitis should be differentiated from systemic photoallergic dermatitis with constant exposure to the culprit.[16]

PHOTOPATCH AND PHOTOPROVOCATION TESTS

For a given chemical substance, to confirm its capability of inducing topical photoallergic dermatitis, a photopatch test may be done. On day 1, UVA and UVB are applied to determine the minimal erythema doses and the chemical substance is placed in duplicate, then the sites are covered.[5] On day 2, the minimal erythema doses are read and one place of the chemical substance is exposed to UVA with a dose of 10 J/cm^2 or 5 J/cm^2 (if the minimal erythema doses are low), then the sites are covered again. On day 3, the sites are read. A positive response at the irradiated site along with a negative response at the nonirradiated site suggests a photoallergic reaction to the chemical substance.

If a chemical substance's capability of inducing systemic photoallergic dermatitis is the subject of investigation, a photopatch test is usually not suitable, since usually a metabolite of the chemical substance instead of its own is responsible for the photoallergy.[16] In this case, a systemic photoprovocation test may be done. First, UVA is applied to a control patch. Then, the chemical substance is administered systemically. When it reaches the maximum level in plasma, UVA is applied to a new patch. After 24 and 48 hours, the patches are read. A positive response at the second patch along with a negative response at the first patch suggests a photoallergic reaction to the chemical substance.

Photopatch and photoprovocation tests with photoirritant chemical substances are positive in the vast majority of subjects.[7] Therefore, they are usually not useful for confirming the etiology of a photoirritant dermatitis.

MANAGEMENT

Management of photosensitive dermatitides should include three measures: elimination of photoreactive chemical substances, photoprotection, and anti-inflammatory or symptomatic treatment.[8,14,16] Not only the culprit, but also other common photoreactive chemical substances should be avoided. Since cross reactions to structurally related agents are possible, a list of cross-reactive substances should also be given to patients with photoallergic dermatitis particularly due to salicylanilides and phenothiazines.[8] Another well-known example for cross-photosensitization is ketoprofen-induced photoallergy.[4,18] This drug may cross-react not only with other nonsteroidal anti-inflammatory drugs such as suprofen and tiaprofenic acid, but also with other drugs containing a benzophenone structure such as a lipid lowering agent, namely fenofibrate. In addition, it has also been reported that ketoprofen may lead to photoallergy to a sunscreen agent, namely octocrylene.

Photoprotection is not only use of sunscreens, but also it requires staying out of the sun and wearing photoprotective garments. Patients should stay indoors particularly during the middle of the day. In severe cases, the patient should be confined in a darkened room for several days, since an ordinary window glass may not filter ultraviolet sufficiently.[8] In getting dressed, the most important principle is to cover the skin as widely as possible. Since it is commonly impossible to cover the face with garments, a broadbrimmed hat or an umbrella should be used to form a shade for the face. Clothes should be densely woven. Contrary to common opinion, white clothes are not more protective, since sunlight may pass through them, if they are wet with water or sweat.[8]

As for use of sunscreens, they must be broad-spectrum and fragrance-free.[16] Physical sunscreens such as titanium dioxide and zinc oxide should be preferred instead of chemical ones.[8,14] They should be applied amply and frequently to exposed-areas. On the other hand, it should be always kept in mind that sunscreen may cause contact allergy and/or photoallergy.

Systemic -often oral- photoprotection is also possible.[19] They may be used as complementary agents to topically applied sunscreens. Carotenoids are well-known examples of such agents. Moreover, nicotinamide, vitamin C, vitamin D, and vitamin E have anti-oxidant properties, so that they may offer photoprotection. There are also dietary photoprotective agents such as green tea and pomegranate. *Polypodium leucotomos* is a fern plant found

in Central and South America. Its extract has been used as a traditional medicine for centuries. Since the beginning of the third millennium, this extract has also been marketed both in Europe and in United States. Besides its anti-oxidant effects, it has also anti-inflammatory and immunomodulatory effects, so that it has been qualified as a "photoimmunoprotective" agent.

In acute cases, photoprotection should be extended beyond recovery of the eczematous reaction, in other words it should be lasted for at least two weeks, since the photoreactive chemical substance is excreted from the skin tardily.[8] As a prophylactic measure, desensitization to sunlight may be possible with repeated short exposures.[8] It is probably due to an increase both in melanin formation and in thickness of the stratum corneum.

As for anti-inflammatory or symptomatic treatment, if erythema and edema is severe in an acute case, cold compresses may be helpful.[8,14] If the clinical presentation resembles an exaggerated sunburn, Aspirin or a nonsteroidal anti-inflammatory drug may be administered as soon as possible for a few days. Eczematous lesions are relieved by emollients and topical corticosteroids. If the reaction is generalized, systemic corticosteroids may be required. If a chronic case is only responsive to systemic corticosteroids, immunosuppressive agents such as azathioprine may be used for its steroid-sparing effect.

Hyperpigmentation following phytophotodermatitis may be resolved with a bleaching cream containing retinoic acid, hydroquinone and hydrocortisone.[16] In refractory cases, Rubin laser therapy may be helpful.

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Systemic Contact Dermatitis

Sistemik Kontakt Dermatit

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ABSTRACT Systemic contact dermatitis is a clinical condition characterized by a delayed-type (type 4) hypersensitivity reaction that develops in individuals previously sensitized to an allergen through the skin, following systemic re-exposure. Systemic contact dermatitis consists of subgroups with similar pathophysiologies. The precise mechanism underlying systemic contact dermatitis reactions has not yet been clearly defined. The disease can be triggered by a wide variety of plants, foods, metals, and medications. Patch testing with suspected agents is recommended for patients who achieve remission after necessary treatment. The primary approach to systemic contact dermatitis treatment is identifying and eliminating the causative allergen. After discontinuing contact with the culprit allergen, skin findings typically regress with desquamation within a few weeks.

Keywords: Contact dermatitis, systemic; patch tests; metal; dermatitis, allergic contact

ÖZET Sistemik kontakt dermatit, deri yoluyla alerjene daha önceden duyarlanmış olan bireylerde sistemik yeniden maruziyet sonrasında gelişen bir gecikmiş tip (tip 4) aşırı duyarlılık reaksiyonu ile karakterize edilen bir klinik durumdur. Sistemik kontakt dermatit, benzer patofizyolojilere sahip alt gruplardan oluşur. Sistemik kontakt dermatit reaksiyonlarının kesin mekanizması henüz net bir şekilde tanımlanmamıştır. Hastalık, çeşitli bitki, gıda, metal ve ilaçlar tarafından tetiklenebilir. Tanıda uygun tedavi sonrasında remisyon elde edilen hastalara şüpheli ajanlarla yama testi önerilir. Tedavide temel yaklaşım, sebep olan alerjeni tanımlamak ve ortadan kaldırmaktır. Tetikleyici alerjenle temas kesildikten sonra, deri bulguları genellikle birkaç hafta içinde deskuamasyon ile gerileme eğilimindedir.

Anahtar Kelimeler: Kontakt dermatit, sistemik; yama testleri; metal; dermatit, alerjik kontakt

Systemic Contact Dermatitis (SCD) is a clinical condition, characterized by a delayed-type (type 4) hypersensitivity reaction that develops in individuals previously sensitized to an allergen through the skin, following systemic reexposure. Systemic exposure routes include oral, intravenous, intramuscular, intranasal, rectal, subcutaneous, intraarticular, intravesical, and inhalation. SCD consists of subgroups with similar pathophysiologies.[1] The precise mechanism underlying SCD reactions has not yet been clearly defined. Although the pathophysiology of SCD is mainly based on patients sensitized to the metals, these results cannot be definitively extrapolated to drug-elicited reactions, even hough the mechanisms are thought to be similar. While Allergic contact dermatitis (ACD) has been described as a type IV delayed-type hypersensitivity, SCD may also involve a type III immune response, as antigen-antibody complexes have been found in the skin, and in the blood.[1,2]

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TABLE 1: Clasification criterias of systemic drug-related intertriginous and flexural exanthema.[6]

Initial or repeated systemic drug exposure
Erythema in the inguinal and/or gluteal area
Additionally, erythema in other flexural areas
Symmetrical distribution
Absence of systemic symptoms and findings

DEFINITIONS

Nakayama et al. reported a series of 15 cases in 1983 and defined it as mercury exanthema. The cases occur in the form of sharply circumscribed erythema development in major flexural areas as a result of inhalation of mercury vapor released from a broken thermometer or inhalation of mercury vapor during a dental examination.[3]

In 1984, Andersen et al. defined three cases with similar clinical features, in which the responsible allergens were nickel, mercury, and ampicillin, as Baboon syndrome (BS). They named this specific eruption, which is sharply circumscribed erythema, especially in the gluteal region and flexural areas, as it resembles the buttocks of 'Baboon' monkeys.[1,3] In the initial definitions of Anderson et al., metals and drugs were included in the etiology, but the list was expanded later.[4] Miyahara et al. divided BS into subgroups according to the type of sensitization and agents as classical BS, topical drug-induced BS, systemic drug-induced BS, and SDRIFE.[5]

SYSTEMIC DRUG-RELATED INTERTRIGINOUS AND FLEXURAL EXANTHEMA (SDRIFE)

SDRIFE was described by Hauserman et al. in 2004.[6] Diagnostic criteria are summarized in Table 1. It is a distinctive condition that includes diagnostic criteria and is drug-induced. It is observed in response to antibiotics, especially beta-lactam and aminopenicillins.[1,6]

ALLERGIC CONTACT DERMATITIS SYNDROME (ACDS)

Ozkaya suggested a subclassification based on the causative agent and previous sensitization. They used the group names: contact allergen-induced BS, contact allergenic drug-induced BS, and non-contact allergenic drug-induced BS. The last group is synonymous with SDRIFE.[7]

SYSTEMIC NICKEL ALLERGY SYNDROME (SNAS)

It is a cutaneous reaction after parenteral exposure to nickel and is a subtype of SCD. Symptoms can range from generalized dermatitis to SDRIFE-like cutaneous reactions.[1,8]

EPIDEMIOLOGY

The prevalence of ACDS in the general population is not precisely known because many allergens cause SCD, and the clinical manifestations can vary widely, However, it is estimated to be less common than ACD.[1,9]

A meta-analysis of 17 studies on oral nickel exposure revealed that 1% of nickel-sensitive patients may exhibit a systemic response to daily nickel exposure (0.22-0.35 mg nickel) and 10% may react to a diet consisting of nickel-rich foods (estimated at .55–1.33 mcg nickel). SNAS, characterized by nickel-triggered systemic contact dermatitis with extracutaneous findings, was diagnosed in 98 (5.78%) out of 1696 patients in a study conducted in an allergy unit in Italy.[9]

ALLERGENS AND SENSITIZATION

Sensitization with contact allergens is common in the population. Two large population studies conducted in Denmark, reported positive patch test results with the European standard series at 15.2% and 18.6%. Allergens causing SCD are widespread in our environment. However, due to their diverse clinical appearances and diagnostic challenges, dermatologists may not always diagnose them adequately. Sufficient amounts of molecules transferred transcutaneously and transmucosally can lead to SCD development through these routes.[10]

SCD can be caused by a wide variety of plants, foods, metals, and medications. Common plants and foods include balsam of Peru (BOP), propolis, chamomile, aspartame, urushiol, propylene glycol, and potassium sorbate. Metals known to cause SCD include nickel, chromium, gold, mercury, zinc, and chromium. Medications frequently associated with SCD include various antibiotics and oral and topical steroids.[1,11]

METALS

Elemental metals in food and water are significant causes of SCD depending on the dose. Adjusting the diet to a low amount appears to be effective in the treatment of SCD. Metal-containing cannulas may cause SCD in metal-sensitive patients.[12]

MERCURY

Mercury is still used in topical antiseptics in some countries worldwide. Symptoms may occur in sensitive individuals when inhaling vapor from a broken mercury thermometer.[10] The development of baboon syndrome has been reported as a result of inhaling mercury released from an accidentally broken thermometer.[12]

NICKEL

Patients are typically sensitized to nickel through exposure to jewelry, coins, clothing, and nickel-plated objects. Systemic exposure routes include oral (diet, kitchen utensils used for meals, orthodontic instruments), intravenous (catheter), and through metal implants and stents. Another important exposure route is transcutaneous, through trouser buttons or belt buckles, especially in humid and hot climates.[1,12]

Nickel is found in many foods, especially tea, canned foods, and seafood. The most common SCD triggered by orally ingested nickel is vesicular hand eczema. Therefore, some authors advocate low nickel diet for patients with resistant hand eczema who test positive for nickel in the patch test.[10]

Canned foods contain high amounts of nickel, and dietary avoidance is recommended for nickel sensitive individuals.[12] Nickel-sensitive patients may benefit from low-nickel diets. Tap water contains nickel, which may leach into the water waiting in the pipes. Several liters may be drained before drinking, or bottled water may be preferred.[3] Cooking in stainless steel pots and pans should be avoided as nickel can leach into foods. Processed and canned foods contain more nickel due to packaging.[9]

COBALT

Cobalt is found in the structure of vitamin B12. There are reported cases of SCD with synthetic B12 forms of cyanocobalamin and hydroxycobalamin. Cigarette smoking causes cobalt exposure.[9] The development of pigmented systemic contact dermatitis has been reported after ingestion of vitamin B12 containing cobalt.[12] Exposure to cobalt may occur through diet or intramuscular vitamin B12.[10] Clinical presentations of cobalt-induced SCD include dyshidrotic eczema flares and generalized eczematous eruptions.[1]

CHROMIUM

While cooking in aluminum pots reduces the chromium content of foods, cooking in stainless steel pots increases the chromium content.[9] There are a few reported cases of the development of generalized eczematization due to inhalation of chromium from welding fumes. In individuals with chromium allergy, intake of chromium picolinate and chromium chloride, found in multivitamin tablets and syrups, may trigger generalized dermatitis.[12]

IMPLANTS

Among the implants that cause SCD, the most common are orthopedic implants, often made of stainless steel, metal alloys, or titanium. The most important allergens in orthopedic implants are metals such as nickel, cobalt, chromium, palladium, and titanium. In addition to the metals in the implant, antibiotics and methyl methacrylate it contains may also cause SCD. In most cases, generalization begins in the skin near the implantation site.[13]

ORTHOPEDIC IMPLANTS

Among the implants that cause SCD, the most common are orthopedic implants which are often made of stainless steel, metal alloys, or titanium. The most important allergens in orthopedic implants are metals such as nickel, cobalt, chromium, palladium, and titanium. In addition to the metals in the implant, the antibiotics and methyl methacrylate it contains may also cause SCD. In most cases, generalization begins in the skin near the implantation.[12]

DENTAL IMPLANTS AND PROSTHESES

Dentures, dental fillings, dental crowns, and orthodontic materials contain various metals that can be released into the body and cause SCD. In most cases, no lesions are observed on the oral mucosa despite direct contact with the allergen. Although dental prostheses are widely used, the incidence of SCD is low. Steel and other metals are used to make dental materials. Titanium very rarely causes allergic reactions and is considered biocompatible for use in implants. However, cases of SCD have been reported.[12]

OTHER IMPLANTS

Although uncommon, cases of SCD have been reported with pacemakers and endovascular stents. Intrauterine devices often contain copper. Although copper hypersensitivity is rare, cases of SCD have been reported.[12,14]

PLANTS AND HERBALS

Allergens in this group; Peruvian balsam, urishiol, garlic, and sesquiterpene lactones.[10]

BALSAM OF PERU

Patients sensitive to the balsam of Peru may develop SCD with products such as spices, ketchup, tea, ice cream, cola, cough syrup, lozenges, and toothpaste.[10] Common allergens include Peru balsam, garlic, propolis, composite family (chamomile tea and other products), and cashew nuts.[12] Found in perfumes and causes SCD through inhalation, it is also present in medicine and as a flavoring in many foods. Cross-reactivity with vanillin, citrus, cinnamon, garlic, and tomatoes is common.[1] Balsam of Peru is found as a sweetener in many foods and beverages, and its elimination from the diet is recommended for patients at risk of SCD. Generalized eruptions may be observed after ingesting cashew nuts in patients sensitized to poison ivy.[12,15]

PROPOLIS

Propolis, a resin compound obtained from the sap of various trees and plants, is related to BOP. Used by bees in making hives and called bee glue, it is an ingredient in products such as toothpaste, lozenges, soaps, and lotions. It has been shown to cross-react with BOP through patch testing.[1,16]

DAISY

A plant from the composite family, daisy contains sesquiterpene lactone, playing a crucial role in the plant's metabolism. These molecules bind strongly to haptens, explaining their role in SCD pathogenesis. Common symptoms include cheilitis, stomatitis, and lip swelling.[1]

FOOD ADDITIVES

Aspartame

Aspartame is a widely used artificial sweetener. It is metabolized to formaldehyde in the body and may cause SCD in people sensitive to formaldehyde.[12] Aspartame has been reported in a small number of patients who consumed large amounts of products such as low-fat foods and diet sodas. The most common presentation is eyelid dermatitis.[1] It is a metabolized product of aspartame and avoidance of aspartame should be recommended in people sensitive to formaldehyde. Products containing aspartame; protein powders and bars, diet drinks including soda, and low-calorie or sugar-free foods.[9]

Propylene Glycol

Chosen as the allergen of the year in 2018 by the American Contact Dermatitis Association, propylene glycol is widely used in meals and cosmetics.[12]

Paraben

Used as a preservative with low allergenicity, paraben is found in pickles, ready-made baked goods, syrup, and jelly/jam/marmalade.[9]

Sorbic Acid

Sorbic acid is commonly found as a preservative in prepackaged foods, including some packaged dairy and meat products.[9] It is naturally present in some fruits and used as a preservative in various foods and products. For individuals sensitized to sorbic acid through cutaneous exposure, SCD may develop upon subsequent oral consumption of fruits containing sorbic acid, such as cranberries and strawberries.[17]

Medicines

Ointments containing anesthetics used in the treatment of hemorrhoids and during rectal examination. Cases of SCD have been reported with local anesthetics such as tetracaine and enemas containing NSAIDs such as aminosalicylic acid.[12] SCD can also be triggered by contact with the vaginal mucosa. A case of SDRIFE developed with metronidazole suppository has been reported.[11] Neomycin a common cutaneous sensitizer, and SCD may develop in patients systemically exposed to other aminoglycosides such as gentamicin. In patients sensitized after the use of topical steroids, SCD may occur with systemic exposure to the same or cross-reactive group of steroids.[6] SCD has been reported with prednisone and dexamethasone.[10]

In a review on SCD cases caused by topical and systemic drugs, 104 reactions were reported in 95 patients with 41 topically applied drugs (in some cases, there was more than one manifestation). In 51 cases (49%), the culprit drug was administered through the mucosa. In applications on mucosa, the most frequent notification was via inhalation. In 35 cases (33.7%), the drug was applied to the skin. 16 cases (15.4%) were applied to both skin and mucosa (anal/perianal). The most reported drugs are; budesonide (23 cases), bufexamac (17 cases), and dibucaine (8 cases). Only 1 reaction was reported for 24 drugs (59%). The most common clinical pictures in SCD cases that develop after topical medication are; It is dermatitis in 34 cases (32.7%), SDRIFE in 12 cases (11.5%), and maculopapular eruption in 10 cases (9.6%).[18]

279 reactions were reported in 240 patients with 95 systemically administered drugs. Of the 279 reactions, 192 (68.8%) occurred orally, the most frequently reported

drugs were mitomycin C (29 cases, 10.4%), methylprednisolone (21 cases, 7.5%), and hydrocortisone (20 cases, 7.2%).

The most common clinical presentations in SCD cases that developed after systemic medication are; Dermatitis in 59 cases (21.1%), maculopapular eruption in 35 cases (12.5%), exacerbation at the site of previous positive patch test in 26 cases (9.3%), SDRIFE in 22 cases (7.9%), erythrodermia or erythematous eruption in 17 cases (6.1%). Exacerbation at the previous dermatitis site and positive patch test site were observed more frequently in the drug provocation group compared to the non-provocation group.[18]

CLINICAL FEATURES

Cases of SCD can present in various clinical forms and these clinical conditions may coexist (Table 2). It typically develops within hours to 2 days after systemic exposure to the allergen, and the lesions follow a symmetrical course.[10,19] Patients may experience subjective symptoms such as itching and burning, while systemic symptoms are rarely observed.[10] The most common forms of SCD are eczematous flares, and flare-ups in areas of previous dermatitis following allergen exposure are where the clinical picture is most severe, even though the reaction is common.[20] Vesicular hand eczema has been associated with oral intake of nickel, cobalt, and chromium in particular.[9,20]

TABLE 2: Symptoms and findings seen in systemic contact dermatitis.[18-20]

Eczematous flare in areas of previous dermatitis or applied patch test
Worsening of existing eczema
Vesicular hand eczema (Dyshidrotic eczema)
Eczematous eruption (Common, generalized)
Maculopapular eruption
Flexural dermatitis
Baboon syndrome/SDRIFE
Vasculitis-like lesions
Urticarial lesions
Purpuric lesions
Erythema multiforme-like lesions
Erythrodermic
Systemic symptoms: Fever, headache, malaise, nausea, vomiting, diarrhea, arthralgia

The most common histopathological findings in Baboon syndrome and SDRIFE include superficial lymphohistiocytic perivascular infiltration, sometimes be accompanied by neutrophils, eosinophils, and mast cells. Spongiosis in the epidermis may or may not be accompanied. Hydropic degeneration with scattered necrotic keratinocytes can be observed in the basal layer. Periadnexal infiltration may also occur, rarely.[10] In cases of SDRIFE, the blood picture is usually normal.[19] Positive patch test results were reported as 50% in SDRIFE patients by Hausermann et al.[6,10] Oral provocation tests have been found positive in almost all SDRIFE cases and seem to be the most reliable way to confirm the diagnosis. Histopathology is nonspecific and is insufficient to confirm the diagnosis of these two entities. Prick test and lymphocyte stimulation test are negative in most cases reported as SDRIFE.[10]

DIAGNOSIS

The diagnosis of SCD, which can manifest with very different clinical presentations, begins with a detailed history and whole-body skin examination, as in other contact dermatitis.[20] SCD is included in the differential diagnosis with a wide variety of diseases. In pediatric cases, especially viral exanthema, impetigo, and staphylococcal scalded skin syndrome should be excluded. Sdrife and allergic contact dermatitis, irritant contact dermatitis, Hailey Hailey disease, pemphigus vegetans, tinea cruris, candidiasis, and inverse psoriasis should be considered in differential diagnoses since they can occur in similar localizations.[1]

PATCH TEST

Patch testing with suspected agents should be performed in patients who achieve remission after necessary treatment. In cases of drug-induced SCD, patch testing is recommended within 6 weeks to 6 months after the reaction.[19] Standard series or customized tests with relevant allergens can be applied depending on the history.[1,21] Some drugs (such as corticosteroids, antimicrobials, antihistamines, anesthetics, and non-steroidal anti-inflammatory drugs) are available in commercially available ready-made forms for patch testing. The European Contact Dermatitis Association has a guide for drugs that do not have a ready-made form. For biomedical devices containing metal, Schalock et al. recommend appropriate metal series according to the patient's history and the type of implant.[21-23]

It's important to note that the experience of the evaluator is crucial in patch testing, as irritant reactions or false-positive results may occur with some metal salts. Oral provocation tests can be performed for a definitive diagnosis with agents found to be positive in patch tests. Although generally considered a safe test due to its late-type reaction, there is a slight risk of an anaphylactic reaction during the oral provocation test, and it should be applied after taking necessary precautions.[1,23] Provocation tests confirm the diagnosis of SCD, and clinical improvement after restricting systemic intake supports the diagnosis.[1,21-23]

PROGNOSIS

The prognosis of SCD with oral exposure is influenced by compliance with the diet. Individual response thresholds may vary, and those who are more sensitive may need to adhere more strictly to the diet.[10]

TREATMENT

The primary approach to SCD treatment is identifying and eliminating the causative allergen. After discontinuing contact with the culprit allergen, skin findings typically regress with desquamation within a few weeks.[1,2]

For symptomatic relief, topical corticosteroids can be used in mild cases, and short-term systemic corticosteroids can be used in severe cases, along with oral antihistamines, depending on the severity of the condition.[2] Based on anamnesis, removing suspected allergens from the diet and seeing whether allergic symptoms regress may serve as an aid to diagnosis. In cases of nickel-related SCD, disulfiram, which is a nickel chelator and is mostly used in alcohol addiction, has been used with varying success rates. In cases where it is not possible to exclude it from the diet and it remains resistant despite steroid treatments, immunosuppressive agents such as azathioprine, cyclosporine, methotrexate, and mycophenolate mofetil can be used.[1] Phototherapy may be an alternative option in difficult cases. Hyposensitization is a new treatment for SCD that involves exposure to increasing amounts of allergens to alter the immune response. Oral hyposensitization may be a treatment option for the SNAS group.[10,24]

In terms of prophylaxis, it's crucial to inform patients about the substances containing detected culprit allergens and ways to protect themselves from them.[20] In children, special considerations include repeated or high consumption of certain foods or condiments like ketchup. Adherence to a low-allergen diet may require the collaboration of both the patient and the parent.[10,25,26]

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Noneczematous Contact Dermatitis

Nonekzematöz Kontakt Dermatit

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ABSTRACT Contact dermatitis usually presents as an eczematous appearance characterized by erythema, edema, vesicles, scales, crusts or lichenification. However, it can sometimes wear many masks, mimicking other skin disease due to its diverse clinical features. These atypical presentations are collectively called non-eczematous contact dermatitis. The most commonly observed forms include erythema multiforme-like, purpuric, lichenoid, lymphomatoid, pigmented, follicular, pustular, bullous, dyshydrosiform, and granulomatous contact dermatitis. Due to its atypical clinical manifestations, the diagnosis of noneczematous contact dermatitis may be challenging and is based on clinical contact history and possitive patch test reaction consistent with the observed clinical findings. In this section, atypical clinical manifestations of contact dermatitis are discussed.

Keywords: Dermatitis, contact; dermatitis; eczema; skin diseases, eczematous; dermatitis, allergic contact

ÖZET Kontakt dermatit çoğunlukla eritem, ödem, vezikül, skuam, kurut veya likenifikasyon bulgularıyla karakterize olan ekzematize görünüm ile karşımıza çıkmaktadır. Nadiren bu bulgulardan farklı olarak başka deri hastalıklarını andırır şekilde farklı klinik bulgular verebilmektedir. Bu farklı tipteki kontakt dermatit non-ekzematize kontakt dermatit olarak bilinmektedir. Eritema multiforme benzeri, purpurik, likenoid, lenfomatoid, pigmente, foliküler, püstüler, büllöz dizhidrotiform ve granulomatoz kontakt dermatit en çok bildirilen nonekzematize formlardır. Atipik klinik görünümden dolayı nonekzematize formların tanısını koymak zor olabilir ve tanı temel olarak hastanın temas hikayesinin olması ve klinik bulgularla örtüşen şüpheli alerjen ile pozitif yama testi sonucu ile konmaktadır. Bu bölümde kontakt dermatitin atipik klinik şekilleri tartışılmıştır.

Anahtar Kelimeler: Dermatit, temas; dermatit; ekzema; deri hastalıkları, ekzematöz; dermatit, alerjik kontakt

Although eczema and dermatitis are often used interchangeably, the term ‘eczematized’ refers to the erythema, edema, vesicles, scales, crusts and lichenification that can be observed differently depending on the stage of the disease.[1] In the acute phase, edema, inflammatory papules, vesicles, or exudate (oozing) are typically seen, while skin dryness, cellular infiltrate, scaling, hyperkeratosis, or fissuring are predominant in the chronic phase. Contact dermatitis exhibits these typical eczema symptoms, but clinical findings may occasionally resemble other skin diseases. Contact dermatitis that manifests with different types is known as ‘noneczematous contact dermatitis. Erythema multiforme-like, purpuric, lichenoid, lymphomatoid, pigmented, follicular, pustular, bullous, dyshydrosiform and granulomatous are the defined types of non-eczematous contact dermatitis (Table 1). The reason for the occurrence of a different clinical findings, other than classical eczema is not fully known, and it is thought that the structural characteristics of the

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TABLE 1: Types of noneczematous contact dermatitis and the substances most commonly associated with these types.

Type of noneczematous contact dermatitis	Related allergens
Erythema multiforme-like (urticarial)	Plants, tropical trees (e.g., Brazilian rosewood, poison ivy), formaldehyde, dinitrochlorobenzene, epoxy, azo dyes, topical medications (e.g., aminoglycosides, ethylenediamine)
Purpuric	Textile dyes, rubber, glues, isopropyl-N-phenyl-p-phenylenediamine (in elastic products), azo dyes, paraphenylene diamine, balsam of Peru
Lichenoid	Phenylenediamine-derived color developers, topical aminoglycoside, epoxy, methylisothiazolinone, white mustard seed, tattoo dyes, metals (e.g., copper, zinc, mercury, palladium, tin)
Lymphomatoid	Rubber compounds, dyes, metals, preservatives, paraphenylenediamine, p-tert-butyl-phenol-formaldehyde resin, ethylenediamine, nickel, cobalt, gold, textile dyes, methylisothiazolinone, methylchlorisothiazolinone, paraben, teak tree, propolis
Pigmented	Optical brighteners, azo dyes, fragrances, rubber compounds, nickel, potassium dichromate, p-tert-butylphenol formaldehyde resin, topical minoxidil, musk ambrette, henna hair dye
Bullous	Cinnamon salt, azo dyes, diethylthiourea, paraphenylenediamine
Pustular	Nitrofurazone, black rubber, isoconazole, fragrances, isothiazolinones
Papular/Follicular	Formaldehyde resin, nickel, chromium, copper, fluoride, selenium salts, tocopherol, polyoxyethylene lauryl ether, methyl glucose sesquistearate, homomentyl salicylate, isothiazolinones
Granulomatous	Metal salts (zirconium, beryllium, palladium, nickel, gold, magnesium), palladium, gold, nickel, zirconium, aluminum salts, tattoo inks, titanium, indium, iron oxide

culprit substances as well as personal factors may play a role. The gold standard test to detect the responsible allergen in these types, as in the eczematous type, is the patch test, and the removal of the responsible allergen is the basis of treatment.[2-5]

ERYTHEMA MULTIFORME-LIKE (URTICARIAL) CONTACT DERMATITIS

Erythema multiforme-like contact dermatitis is the most common clinical type among the noneczematous types. Allergens that cause this type of contact sensitivity are more often plants and tropical trees.[6-10] Dalbergia nigra (Brazilian rosewood), Toxicodendron radicans (poison ivy), Primula obconica, Lysimachia clethroides, Laurus nobilis, Agastache rugosa, Geranium robertianum, Machaerium scleroxylon are some of these trees. Tropical trees are used in our country to make wooden items such as furniture or musical instruments. For this reason, it is more common in professional groups such as carpenters, foresters, joiners who have a lot of contact with trees, or in those who deal with trees and plants as a hobby. it may also be seen for non-occupational reasons as it may be associated with chemicals such as formaldehyde, dinitrochlorobenzene, epoxy, and azo dyes and with topical medications such as aminoglycosides, ethylenediamine, clioquinol, balsam of Peru, and scopolamine.[11-19] Clinically, lesions with erythematous edematous papules are begin on contact area but frequently spread throughout the body as target erythema multiforme-like lesions.[14] Symmetrical acral involvement and mucosal involvement seen in erythema multiforme are not an expected feature. Unlike classical erythema multiforme, the lesions often merge and form large plaques.[15] Although the mechanism of development of these lesions is not fully known, it is thought to occur with the immune complex reaction that occurs after the absorption of the agent that creates contact sensitivity through the skin. Distant areas involvement has frequently been reported. Histopathologically, spongiosis and exocytosis are observed in the epidermis, edema and perivascular lymphocyte infiltration are observed in the superficial dermis. Unlike erythema multiforme, epidermal necrosis and vacuolar degeneration are either absent or minimal. Patch testing with the responsible allergen often results in an eczematous reaction.[3] Contact sensitization should be considered, especially in cases of erythema multiforme without acral or mucosal involvement, and these patients should be questioned about their contact with tropical trees, flowers, or topical herbal oils.

PURPURIC CONTACT DERMATITIS

Purpuric contact dermatitis, often presenting as asymptomatic purpuric patches or plaques, occasionally accom-

panied by erythema in the contact area, can be either irritant or allergic in nature. The allergens most associated with this rare non-eczematous type are textile dyes, rubber, and glues. Isopropyl-N-phenyl-p-phenylenediamine, found in elastic underwear, rubber boots, underwear, diving suits, elastic bandages, and increasingly in widely used smartwatch straps, may induce purpuric contact dermatitis. The diaphoretic and occlusive effects of these elastic products facilitate sensitization. Additionally, azo dyes, paraphenylene diamine, balsam of Peru, optical brighteners, formaldehyde resin, benzoyl peroxide, methylchloroisothiazolinone/methylisothiazolinone, and raw wool are reported agents responsible for pigmented contact dermatitis.[3-5,19,20] In patch tests, eczematous and rarely purpuric reactions are observed with the responsible allergen. The sap of Agave Americana and povidone iodine are the most reported agents causing irritant-type purpuric contact dermatitis.[21,22] In the irritant form, the lesion is limited to the contact area, heals faster, and exhibits less infiltration than the allergic form. Histopathologically, spongiosis, exocytosis, perivascular lymphocytic infiltration, and erythrocyte extravasation are observed in the epidermis, but no vasculitis is evident.[3]

LICHENOID CONTACT DERMATITIS

Lichenoid contact dermatitis, a rare non-eczematous form, presents with clinical and histopathological features similar to lichen planus, occurring in both mucosa and skin. Lichenoid contact dermatitis is more commonly observed on the hands and forearms and has been most frequently reported with phenylenediamine-derived color developers.[3,23]

Eczematized papules and plaques originating in the contact area are accompanied by livid erythematous papules. The initial appearance of eczematous plaques aids in distinguishing lichenoid contact dermatitis from lichen planus. Although livid papules may extend to other skin areas, mucosal involvement is generally absent with dye developers, confining the lesions to the skin. Lichenoid contact dermatitis has been reported after coral contact with topical aminoglycoside, epoxy, methylisothiazolinone, white mustard seed (*Semen Sinapis Albae*) used in acupuncture treatment and may also develop against tattoo dyes.[24-28]

Metals such as copper, zinc, mercury, palladium, and tin are often act as responsible haptens for lichenoid contact dermatitis in the oral mucosa. Clinically, it may appear as reticular plaques or erosions resembling oral lichen lesions.[29,30]

While some cases exhibit typical lichen planus findings histopathologically, chronic dermatitis findings are dominant in most instances. Lichenoid contact dermatitis differs from lichen planus with more prominent spongiosis, less common hypergranulosis, less pronounced vacuolar degeneration and pigment incontinence, perivascular instead of band-shaped lymphohistiocytic infiltrate, and the absence of apoptotic keratinocytes.[3,31] The patient's history of contact with a suspicious substance, eczematous lesions in the initial area, lack of oral mucosal involvement, and histopathologically nonspecific chronic dermatitis findings despite clinical lichen-like appearance are indicative factors for the diagnosis of lichenoid contact dermatitis. Positive reactions in patch testing with the suspected allergen are mostly eczematous; in some cases, positive areas may develop a lichenoid character over time.[3]

LYMPHOMATOID CONTACT DERMATITIS

Lymphomatoid contact dermatitis is an uncommon type of contact dermatitis which simulate cutaneous lymphomas clinically and/or histopathologically. It presents as persistent, erythematous, scaly patches, plaques, or nodules in the area of contact with the allergen. Histopathologically, these lesions exhibit superficial band-shaped T-cell infiltration and epidermotropism, reminiscent of mycosis fungoides. While there is no specific hapten identified as the sole cause of lymphomatoid contact dermatitis, this type is most frequently associated with rubber compounds, dyes, metals, and preservatives.[32] Paraphenylenediamine, p-tert-butyl-phenol-formaldehyde resin, ethylenediamine, nickel, cobalt, gold and textile dyes are the most frequently reported haptens.[3] Cases of lymphomatoid contact dermatitis have also been reported with methylisothiazolinone, methylchlorisothiazolinone, paraben, teak tree, and propolis.[32-35]

Histopathologically, the presence of microvesicles along with spongiosis in the epidermis supports the diagnosis of lymphomatoid contact dermatitis. Conversely, marked epidermotropism, the absence of acanthosis, deep monomorphic infiltration of atypical lymphocytes and monoclonality in gene rearrangement are findings suggestive of mycosis fungoides.[36,37]

The diagnosis is confirmed when the lesions lose their persistent character after removing responsible allergen is detected by patch testing then removed. Long-term follow-up of patients is crucial to avoid overlooking cutaneous lymphomas, which should be considered in the differential diagnosis.

PIGMENTED CONTACT DERMATITIS

Pigmented contact dermatitis has been observed in the aftermath of epidemics caused by whiteners in laundry detergents, with sensitization to certain chemicals, such as pyrazoline derivatives, leading to a clinical presentation dominated by pigmentation.[38] This form of dermatitis is characterized by dark hyperpigmentation with indistinct boundaries, occasionally reticular or mottled, in the area of contact with the allergen. It is more prevalent in individuals with fair skin. Besides optical brighteners, pigmented contact dermatitis can be caused by azo dyes in clothing, fragrances, cosmetics containing 1-phenol-2-naphthol, rubber compounds, nickel, potassium dichromate, p-tert-butylphenol formaldehyde resin, and topical minoxidil, airborne pigmented contact dermatitis with musk ambrette.[38-40] Recently, a case-control study shedding light on significant associations with hair colour usage, especially henna hair dye, among patients having Pigmented contact dermatitis.[41] Pigmented photoallergic contact dermatitis may also occur due to exposure to plants and fragrance substances.[4] Pigmented photoirritant contact dermatitis, associated with fragrance substances containing psoralen, is known as Berloque dermatitis.

BULLOUS CONTACT DERMATITIS

Bullous contact dermatitis is a rare form of contact dermatitis characterized by a predominant presence of blisters in the clinical presentation. This clinical type is more commonly associated with irritant and photoirritant contact dermatitis, but it can also result from contact sensitization. There have been reports of bullous allergic contact dermatitis developing from various sources, including cinnamon salt containing cinnamic aldehyde and cinnamic alcohol applied to wounds, azo dyes in lycra clothes, diethylthiourea in rubber boots, paraphenylenediamine in temporary tattoos, and injections of lidocaine and intra-articular triamcinolone acetonide.[42-48]

It's crucial to note that bullous contact dermatitis can clinically and histopathologically resemble bullous pemphigoid, and when necessary, an immunofluorescence examination should be performed.

The reaction observed in patch tests with the responsible allergen is predominantly eczematous and occasionally bullous. Given the irritant properties of the responsible allergen, it is recommended to conduct the patch test with diluted series to facilitate the differentiation between irritant and allergic reactions.[47]

PUSTULAR CONTACT DERMATITIS

Although sterile pustules seen in the contact area are more commonly associated with an irritant reaction, they can also be a symptom of allergic contact dermatitis. Pustular contact dermatitis has been reported due to exposure to nitrofurazone, black rubber, isoconazole, merbromin, fragrances, isothiazolinones and minoxidil. In some reported cases, follicular-located pustules were observed, while in others, superficial pustules resembling acute generalized exanthematous pustulosis developed.[49-51] During patch tests, some patients exhibited a pustular response instead of the classical eczematous response.[3]

PAPULAR/ FOLLICULAR CONTACT DERMATITIS

This type of contact dermatitis clinically presents with predominantly itchy, small papules located around hair follicles, and can be either irritant or allergic in nature. Histopathologically, perivascular lymphocytic infiltration is observed surrounding spongiosis in the follicle, eccrine sweat gland epithelium, and skin appendages in the dermis. The interfollicular area remains unaffected.[52,53] Reported allergens causing follicular allergic contact dermatitis include formaldehyde resin, nickel, chromium, copper, fluoride, and selenium salts found in non-ironing textile materials, as well as tocopherol, polyoxyethylene lauryl ether, methyl glucose sesquistearate, homomentyl salicylate, and isothiazolinones in cosmetic products. The formation of follicular contact dermatitis is believed to be influenced by factors such as the patient's atopic structure, sweating, friction, and pressure, in addition to the structural characteristics of the contact material.[52-55]

Like other forms of contact dermatitis, patch testing with the suspected allergen is essential for patients with a suggestive history and clinical findings of follicular contact dermatitis. A positive response in the patch test may manifest as classical eczematous reactions or follicular papules observed in the clinical setting.[54]

GRANULOMATOUS CONTACT DERMATITIS

Granulomatous type contact dermatitis is characterized by granulomatous papules, plaques or nodules resembling sarcoidosis, sometimes accompanied by slight itching. Granulomatous late hypersensitivity reaction can occur in response to metal salts such as zirconium, beryllium, palladium, nickel, gold, and magnesium. This reaction occurs when allergens come into contact with damaged skin rather than the normal skin surface.[3-6]

In recent years, the hapten most frequently reported to cause granulomatous contact dermatitis is palladium, primarily exposed through metal piercing and earring use.[56,57] Gold and nickel can also cause granulomatous contact dermatitis in a similar manner.[58] Zirconium and aluminum salts found in deodorants can cause this reaction, especially in the axillary region which is prone to abrasion due to epilation or friction, allowing the metal salts to penetrate the skin, causing a granulomatous reaction. Other reported causes include tattoo inks, titanium in pacemakers, indium in dental alloys, and iron oxide.[4,59-60]

Histopathologically, it is not possible to distinguish granulomatous contact dermatitis from sarcoidosis. The location of the lesions is the most important feature leading to the diagnosis of contact dermatitis. A patch test performed with the suspected allergen reveals an eczematous reaction. Since late reaction is more common in this type, evaluation should be made on the seventh day. In some patients, the reaction is only possible through skin abrasion. Therefore, in cases where the classical test is negative, a closed scratch test with the suspected allergen or an intradermal test with metal salts in diluted concentration can be performed. In the closed scratch test, the allergen is placed on the scratched skin without causing bleeding and it is covered for 48 hours. A brown-red papule is expected to develop at the test site within 4 weeks. Histopathological findings of sarcoidal granuloma are observed in these papules.[4,5] Even if the suspected allergen is avoided, recovery takes longer compared to the eczematous form.[3-6]

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Occupational Contact Dermatitis

Mesleksel Kontakt Dermatitler

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ABSTRACT Occupational diseases are recognized as an important health problem today. Occupational contact dermatitis is caused by contact with various physical, chemical and biological substances in the work environment and accounts for 90-95% of occupational skin diseases. The most common occupational contact dermatitis are irritant contact dermatitis (ICD), allergic contact dermatitis (ACD) and contact urticaria. Other types of occupational dermatitis are less common, but prevention measures and treatment are based on the same principle. Occupational contact dermatitis is more common in the 4th decade and in males. The most common type of occupational contact dermatitis is ICD. The hands are affected in 90% of cases of occupational contact dermatitis. The occupational groups where ICD is most common are health, cleaning, hairdressing or occupational groups with exposure to chemicals such as metal working fluids. Allergic contact dermatitis is common in agricultural workers, hairdressers, construction workers, rubber and textile workers. In the management of occupational contact dermatitis, avoidance of irritants and allergens is the main principle in mild cases.

Keywords: Dermatitis, irritant; dermatitis, occupational; dermatitis, contact

ÖZET Meslek hastalıkları günümüzde önemli bir sağlık sorunu olarak kabul edilmektedir. Ülkemizde meslek hastalıkları beş ana grupta incelenmektedir. Mesleki kontakt dermatitler; iş ortamındaki çeşitli fiziksel, kimyasal ve biyolojik maddelerin temasına bağlı olarak ortaya çıkmaktadır ve mesleki deri hastalıklarının %90-95'ini oluşturmaktadır. En sık gözlenen mesleki kontakt dermatitler irritan kontak dermatit (İKD), allerjik kontakt dermatit (AKD) ve kontakt ürtikerdir. Mesleki kontakt dermatitler daha çok 4. dekadda ve erkeklerde görülmektedir. En sık görülen mesleki kontakt dermatit tipi irritan kontakt dermatittir. Mesleki kontakt dermatit olgularının %90'ında eller etkilenmektedir. İrritan kontakt dermatitin en yaygın görüldüğü meslek grupları sağlık, temizlik, kuaförlük veya metal işleme sıvıları gibi kimyasal maddelere maruziyeti olan meslek gruplarıdır. Alerjik kontakt dermatit tarım işçileri, kuaförler, inşaat işçileri lastik ve tekstil işçilerinde sık görülmektedir. Mesleksel kontakt dermatit yönetiminde hafif vakalarda irritan maddeler ve alerjenlerde kaçınmak temel prensibi oluşturmaktadır.

Anahtar Kelimeler: Dermatit, irritan; dermatit, mesleki; dermatit, temas

Occupational diseases are recognized as an important health problem today. Occupational diseases are the common name of the diseases that occur due to risk factors in the working environment. According to the World Health Organization (WHO), occupational diseases are not only known and accepted occupational diseases, but also diseases in which the working environment and the way of working are an important factor among other causes in their formation and development. The Italian physician Dr. Bernardini Ramazzini, who wrote the first comprehensive book on occupational diseases, "De Morbis Artificum Diatriba", is today considered the pioneer of occupational health. In this work, Ramazzini discussed 53 different diseases in detail, and also emphasized methods of protection from occupational diseases, healthy nutrition and hygiene rules. Ramazzini was the first physician to add the question "what is your

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profession?" to the questions a physician should ask when examining a patient for the first time.[1,2]

In our country, occupational diseases are analyzed in five main groups: Group A (Occupational diseases caused by chemical substances), Group B (Occupational skin diseases), Group C (Pneumoconiosis and other occupational respiratory diseases), Group D (Occupational infectious diseases) and Group E (Occupational diseases caused by physical factors). Skin diseases that develop as a result of irritation or sensitivity of the skin due to a person's work, the tools and materials used or the working environment are generally called occupational skin diseases. According to the International Labor Organization, occupational skin diseases fall under four main categories. These categories include allergic contact dermatitis and urticaria caused by occupational exposures, irritant contact dermatitis caused by occupational exposures, vitiligo caused by occupational exposures, and other skin diseases caused by physical, chemical or biological agents in the workplace. In many developed countries, including the European Union, occupational skin diseases are the second most common occupational disease after occupational musculoskeletal diseases; however, according to the data for 2019, only 21 (1.9%) of the 1091 diagnosed occupational diseases in our country were categorized as occupational skin diseases.[3-6]

According to ÇASGEM*, skin diseases in Turkey are classified as in Table 1.[7,8]

Occupational contact dermatitis is caused by contacting with various physical, chemical and biological substances in the work environment and accounts for 90-95% of occupational skin diseases. The most common types of occupational contact dermatitis are irritant contact dermatitis (ICD), allergic contact dermatitis (ACD) and contact urticaria. Other types of occupational dermatitis are less common, but prevention measures and treatment are based on the same principle. Occupational contact dermatitis is more common in the 4th decade and in males. The hands are the major affected area, consisting of the 90% of cases of occupational contact dermatitis.[8]

Occupational contact dermatitis is analyzed under the headings of irritant contact dermatitis, allergic contact dermatitis and contact urticaria.

TABLE 1: Classification of occupational skin diseases in Türkiye by ÇASGEM*

Skin Cancers	Skin Diseases other than Skin Cancer
Squamous Cell carcinoma	Contact dermatitis
Basal Cell carcinoma	Acneiform diseases
Specific types of Melanoma	Pigmentation disorders
	Photosensitivity
	Contact Urticaria
	Radiodermatitis

*ÇASGEM: Labor and Social Security Training and Research Center.

IRRITANT CONTACT DERMATITIS

Irritant contact dermatitis (ICD) is a non-specific skin response to direct chemical skin damage and/or the release of inflammatory mediators. Irritant contact dermatitis can occur in acute and chronic forms. Acute lesions of ICD can occur after exposure to a substance (even in small concentrations), the effects can accumulate due to repeated exposure and often lead to chronic skin damage and skin lesions.[9]

Occupational ICD is associated with factors such as chemical exposure, soluble oils and metalworking fluids (MWF), wet processes, detergents, glove use, food, plant contact and mechanical friction. The occupational groups where irritant contact dermatitis is most common; are health, cleaning, hairdressing or occupational groups with exposure to chemicals such as MWF. It is most commonly seen in the hands and rarely in localizations such as face and eyelids. Common causes of irritant contact dermatitis and related occupational groups are shown in Table 2.[8,10]

Acute irritation occurs as a result of exposure to highly alkaline substances or strong acids. The consequences of acute irritation following such exposures usually depend on the concentration of the substance, the duration of contact and the type of chemical. Strong irritant chemicals can cause serious damage to the skin, causing severe damage to the epidermis and direct cellular toxicity. Therefore, different proinflammatory cytokines (e.g. interleukin 1 and tumor necrosis factor-a) are released and contribute to inflammation.

Chronic cumulative ICD is the most common form of occupational ICD. Continuous exposure to mild irritants (e.g. water, soaps, solvents, oils) causes the skin to become reactive to chronic friction and repeated microtrauma. This results in low levels of stratum corneum lipid degradation and loss of cellular cohesion, desquamation and increased transepidermal water loss.[11]

The clinical lesions of acute ICD are usually sharply circumscribed and asymmetrical. In the acute form, erythematous, vesicular, pustular and bullous lesions are usually seen. The lesions are painful and itchy, while usually limited to contact areas. Chronic contact dermatitis is also

TABLE 2: Causes of irritant contact dermatitis and occupational groups.[8]

Factors	Occupational Groups
Detergent, soap, water, solvents	Housewives Cleaning workers Hairdressers Health Workers
Acids, alkalis (formalin, ethylene oxide)	Cleaning workers Laborers
Decomposition oils	Mechanical industry workers
Paper and paper products	Printmakers
Dust particles, cement, fiberglass particles	Construction workers
Formaldehyde	Dyers Textile industry workers Anatomy, pathology laboratory workers
Oxidizing agents (chlorine dioxide), peroxides	Battery manufacturing Hairdressers



FIGURE 1: Chronic irritant contact dermatitis presenting with desquamation, lichenification and fissures.

usually asymmetric. Chronic form is characterized by desquamation, lichenification and fissuring. Likewise in this form, lesions are usually limited to contact areas (Figure 1).[9]

Patients with occupational irritant contact dermatitis give an anamnesis that the lesions started or worsened after starting work and that the complaints regressed on days off.

ALLERGIC CONTACT DERMATITIS AND CONTACT URTICARIA

Allergic contact dermatitis (ACD) is caused by the activation of T cells against a specific allergen and is a late type IV hypersensitivity reaction. The pathogenesis of ACD begins with the binding of a low molecular weight hapten to an epidermal protein. This process initiates the response of the innate immune system and activates skin dendritic cells. Dendritic cells contain the hapten-self protein complex, migrate towards the lymph node and present this complex to T cells, sensitizing them to the allergen. Allergen-specific T cells then proliferate with the development of effector and memory subsets. Upon repeated contact with the allergen, a strong inflammatory response occurs and the clinical picture we call dermatitis emerges.[12]

Allergic contact dermatitis lesions occur within 7-21 days after the first contact with the allergen and within 4 hours after the second contact. There are several different clinical phases in skin lesions of ACD; the erythematous phase with erythema or edema without sharp borders; and the madidans phase with eroded, discharging lesions. In the next phase, crusts and squames appear. Skin lesions are initially asymmetric and limited to the contact area, but often later spread beyond the contact area and become symmetric. Itching is a very prominent symptom in ACD. When the skin lesions of ACD persist, chronic ACD may develop. Skin lesions may occur without an acute phase or may appear over chronic irritant contact dermatitis. Lesions are symmetrical, less sharply circumscribed and distantly spreading. Distant lesions, typically papulovesicular, may also occur. The main feature of chronic ACD is an epidermal reaction with lichenification, fissures and pruritus.[8,9]

Allergic contact dermatitis is common in agricultural workers, hairdressers, construction workers, rubber and textile workers. Common allergic occupational disease allergens and the occupations in which they are seen are shown in Table 3.

Clinically, ACD may be difficult to distinguish from ICD. To make this distinction, a patch test should be performed with possible allergens in the patient's working environment. The more allergens tested in the patch test, the more likely it is to diagnose ACD. If an occupational ACD is suspected, a comprehensive patch test should be performed. There are also commercially available tests that include a range of allergens. Specialized series target specific occupations or chemicals. Examples of specialized series focusing on specific industries or occupations include baking, dentistry, hairdressing, and specialized series focusing on specific chemicals include acrylates, epoxy, isocyanates, metals, oils and coolants, plastics and adhesives, and rubber. If needed, these commercial specific allergen series are also helpful in the diagnosis of occupational allergic contact dermatitis testing.[13]

TABLE 3: Causes of allergic contact dermatitis and occupational groups.[8]

Products	Alergens	Occupational Groups
Accessories containing metal	Nickel, cobalt	Jewelry, belt buckle making sector
Adhesives and surface coatings	Epoxy resin, phenolic, acrylic monomers	Dyers, furniture makers
Clothing, protectors	Formalin	Textile sector
Rubber products	Tiuram	Plastic industry
Latex gloves	Mercaptobenzothiazole	Health workers
Cement	Potassium dichromate	Construction sector
Hair dyes, hair bleachs	Paraphenylenediamine, ammonium persulfate	Hairdressers

Occupational contact urticaria is a less common occupational contact dermatitis compared to irritant and allergic contact dermatitis is the form. Contact urticaria is characterized by itchy wheals that appear suddenly after exposure, within 60 minutes and resolve within 24 hours. It may occur by 2 different mechanisms: immunologic and non-immunologic contact urticaria. Immunologic contact urticaria is an IgE-mediated Type 1 hypersensitivity reaction and non-immunologic form is caused by direct mast cell activation and histamine release.[12]

Non-immunologic contact urticaria usually occurs on first contact, has a milder course and is limited to the contact site. Non-immunologic contact urticaria may develop after contact with benzoic acid, sorbic acid, cinnamic aldehyde, balsam of Peru, nettle, formaldehyde, jellyfish and some fish. Immunologic contact urticaria can cause various clinical scenarios ranging from local reaction to severe anaphylaxis. Immunologic contact urticaria may develop as a result of contacting with latex, proteins of plant origin (apples, kiwi, tomatoes, nuts, celery, peanuts, cereals, spices), proteins of animal origin (salami, sausages, shellfish, animal fluids). Contact urticaria is mostly seen in healthcare workers, veterinarians, pastry cook who come into contact with cinnamic acid, hairdressers, farmers and fishermen. Contact urticaria can be diagnosed by skin prick test.[8,14]

Mathias criteria were established in 1989 to help determine the presence of occupational contact dermatitis. Mathias criteria consist of 7 questions. Answering "yes" to four or more of the questions leads to a 50% or more probability of occupational causation. The Mathias criteria are as follows.[12]

Mathias Criteria

1. Is the clinical appearance compatible with contact dermatitis ?
2. Is there exposure to possible skin irritants or allergens in the workplace ?
3. Is the anatomical distribution of lesions consistent with cutaneous exposure in relation to the work task?
4. Is the relationship between exposure and time of onset of lesions consistent ?
5. Are possible non-occupational causes excluded ?
6. Does the dermatitis improve away from the work environment where exposure to the suspected irritant or allergen occurred ?
7. Has an allergic agent been found by patch or provocation tests ?

MANAGEMENT AND TREATMENT

In the management of occupational contact dermatitis, avoidance of irritants and allergens is the main principle in mild cases. In more severe cases, medium to high potency topical corticosteroids may be given for rapid relief and, if necessary, short courses of systemic steroid therapy. Phototherapy and immunosuppressive drugs can be used in resistant hand contact dermatitis. Antihistamine treatment may be given for itching. In occupational irritant contact hand dermatitis, hands should be washed with warm water and mild unscented soaps or cleansers. The most effective moisturizers are combinations of humectants (topical urea, glycerin) and occlusive emollients (dimethicone, petrolatum), which should be used frequently and before starting work. Gloves should be worn when wet work is necessary, but sweating related the use of gloves may worsen the lesions. Cotton gloves can also be worn under rubber gloves to prevent deterioration due to sweating. The main treatment for occupational ACD is to avoid the causative allergen. The patient should inform the employer and, if possible, work in an allergen-free department.[15]

In contact urticaria, the main treatment is to avoid the substance concerned. Alternatives such as nitrile, neoprene and polyvinyl chloride gloves are recommended for those with natural latex (NRL) allergy. Second generation H1 receptor blockers (e.g. diphenhydramine, hydroxyzine, lo-

ratadine, desloratadine) should be used in the first-line treatment of immunological contact urticaria. Aspirin and NSAIDs are the first-line treatment options in the management of nonimmunological contact urticaria. Patients with a history of contact urticaria should carry subcutaneous epinephrine pens. Steroids are the second-line treatment option and immunosuppressive agents such as cyclosporine and methotrexate may be used in severe cases.[16]

CONCLUSION

In conclusion; occupational contact dermatitis continues to be prevalent among workers and significantly affects quality of life and workability. In general, improving the level of occupational hygiene, including personal protective equipment, can reduce the prevalence of occupational contact dermatitis. Another important point in the prevention of occupational contact dermatitis is that high-risk occupational groups, especially healthcare workers and hairdressers, need a special approach. Standards and guidelines to improve the education, knowledge, diagnosis and multidisciplinary management of occupational contact dermatitis have recently been published and should be routinely implemented.[17]

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Hand Eczema

El Ekzemaları

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ABSTRACT Hand eczema, one of the most frequent dermatological conditions, comprises a heterogeneous group of disorders caused by acute or chronic inflammation of the hands due to various etiological factors such as contact allergens, irritants, and proteins. It is highly prevalent, and some professions, such as hairdressers and healthcare providers, are at higher risk for hand dermatitis. It is classified according to etiology and clinical features. The mainstay of the treatment for all types of hand eczema is protective measures, i.e., the use of emollients and protective gloves, patient education, and avoidance of relevant allergens. The epidemiology, etiology, clinical features, and management of hand eczema will be discussed in this chapter.

Keywords: Skin diseases, eczematous; dermatitis, allergic contact; dermatitis, contact; dermatitis, irritant; dermatitis, occupattional; eczema, dyshidrotic

ÖZET En sık görülen dermatolojik hastalıklardan biri olan el ekzeması, kontakt alerjenler, irritanlar ve proteinler gibi çeşitli etyolojik faktörlere bağlı olarak ellerde görülen akut ya da kronik inflamasyona bağlı heterojen bir grup hastalık tablosudur. Prevalansı oldukça yüksektir. Sağlık çalışanları ve kuaförler gibi bazı meslek grupları, el ekzemaları açısından yüksek risk grubundadır. El ekzemaları etyolojik ve klinik özelliklerine göre sınıflandırılır. Tüm el dermatiti tablolarında tedavinin ilk basamağı; emolyent ve koruyucu eldiven kullanımı, hasta eğitimi ve ilişkili alerjenlerden kaçınılması gibi koruyucu önlemlerin alınmasıdır. Bu bölümde, el ekzemalarının epidemiyolojisi, etyolojisi, klinik özellikleri ve yönetimi tartışılacaktır.

Anahtar Kelimeler: Deri hastalıkları, ekzematöz; dermatit, alerjik kontakt; dermatit, temas; dermatit, irritan; dermatit, mesleki; ekzema, dishidrotik

Hand eczema, or hand dermatitis, is an acute or chronic inflammatory skin condition located on the hands or wrists that may be caused by various etiological factors.[1] It is one of the most frequent causes of dermatology consultations, affecting a considerable proportion of the population. Hand eczema is one of the major occupational disorders, and it has a high psychosocial and economic impact. Economically, hand eczema may lead to lost workdays, medical expenses, and requirements for job changes and replacements.[2] Psychosocially, subjective symptoms, such as itching, burning, and pain, and objective symptoms, such as erythema and scaling, may lead the patient to refrain from social and sportive activities, causing social isolation and mood and sleep disturbances.[3] In this chapter, we will discuss the epidemiology, etiology, clinical features, and management of hand eczema.

EPIDEMIOLOGY AND RISK FACTORS

Hand eczema is one of the most common dermatological disorders, with a lifetime prevalence of up to 15% in the general population.[4] A meta-analysis performed in 2020 re-

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vealed a prevalence of 14.5% in adults and 8.9% in adolescents.[5] The same study showed a pooled incidence of 7.3 cases/1000 person-years.

In both adult and adolescent populations, hand eczema is more frequent in females, with a female-to-male ratio of 1.5-2.[5] The higher prevalence of this entity in females can be explained by the increased hygiene behavior (i.e., more frequent handwashing) and wet work (such as domestic chores) performed by women instead of physiological differences between the two genders.

Individuals from several occupations are at a higher risk for the occurrence of this disease. Hairdressers have a pooled lifetime prevalence of 38.2% with a rate of atopic dermatitis comparable to the general population, suggesting that occupational exposure is the main risk factor for this population.[6] Healthcare workers are another occupational group with a higher tendency to get hand eczema.[7] A study from Türkiye revealed a 12-month prevalence of 45.9% in healthcare workers. Atopic dermatitis, frequent hand washing, and using powdered gloves were among the risk factors for getting hand dermatitis.[8] The COVID-19 pandemic has had an impact on the incidence of hand eczema among health providers. Studies conducted in Northern Italy and Germany during the COVID-19 pandemic showed an increased prevalence of hand eczema symptoms among healthcare workers.[9,10] Professional cleaners are also at a higher risk of developing hand dermatitis, with a self-reported lifetime prevalence of 30.3%.[11]

The most important risk factor for hand eczema is having been diagnosed with atopic dermatitis.[11,12] Atopic dermatitis has been implicated in hand dermatitis in adolescents, healthcare workers, and the general population.[7,12-14] Other lifestyle factors have also been linked with this disease, such as wet work, smoking, frequent handwashing, using alcohol-based hand disinfectants, and wearing gloves in everyday life.[7,14,15] Cold and dry weather conditions may also facilitate the disease by impairing epidermal barrier function.[16] Having any type of contact allergy with a positive patch test is a significant risk factor for hand eczema.[3]

ETIOLOGY, CLINICAL PRESENTATION AND CLASSIFICATION

Hand eczema is not a distinct entity but consists of a heterogeneous group of disorders with different pathophysiologic backgrounds and clinical findings. Classification of this disease is essential to determine the etiology and optimize the treatment for the individual with hand eczema.



FIGURE 1: Acute hand dermatitis. Intensely itchy erythematous papules and coalescing vesicles on the hand dorsum. From the photography archive of Gazi University Faculty of Medicine, Department of Dermatology.

Acute hand eczema is defined in the European Society of Contact Dermatitis (ESCD) Guidelines as dermatitis in the hands and wrists lasting for less than three months and occurring not more than once per year.[17] It mainly presents with edema, papules, and vesicles on an erythematous base (Figure 1). Chronic hand eczema, in turn, is the presence of symptoms for over three months or recurring twice or more yearly.[18] Scaling, fissures, and lichenification are the main clinical features of chronic hand dermatitis (Figure 2).



FIGURE 2: Chronic irritant contact dermatitis. Erythema, hyperkeratosis, and lichenification on the hand dorsi, fissures on interdigital spaces. From the photography archive of Gazi University Faculty of Medicine, Department of Dermatology..



FIGURE 3: Allergic contact dermatitis. Erythematous papules on the flexor aspect of the wrist, caused by the metal attachment of a watchband. From the photography archive of Gazi University Faculty of Medicine, Department of Dermatology.



FIGURE 4: Atopic hand dermatitis. Erythematous, excoriated scaly plaques on the hand dorsal aspect of the hand and fingers in a child. From the photography archive of Gazi University Faculty of Medicine, Department of Dermatology.

Since the clinical presentation of hand dermatitis does not necessarily reflect the etiology of the disease, the ESCD has classified this entity separately according to the etiology and clinical features. The etiological subtypes consist of irritant contact dermatitis (ICD) (Figure 2), which is the most common etiological factor, allergic contact dermatitis (ACD) (Figure 3), atopic hand eczema (Figure 4), and protein contact dermatitis (Table 1). Additionally, chronic hand eczema may be idiopathic in 20% to 26% of the patients. Idiopathic hand eczema is usually associated with concurring plantar eczema.[19] The clinical subtypes have been divided into hyperkeratotic hand dermatitis, acute recurrent vesicular hand eczema (previously known as dyshidrotic eczema or pompholyx), nummular hand dermatitis and pulpitis (fingertip eczema) (Figure 5, Figure 6, Table 2).[17]

In addition to these classifications, hand eczema can be classified according to the source of the cause (Table 3).[3] Any hand eczema caused by professional exposure is classified as occupational hand eczema.

The assessment of the severity of hand dermatitis is vital for optimizing the individual treatment modalities in the clinical setting, as well as for determining the effectiveness of new medications in the research setting. The most commonly used tool for assessing hand eczema severity is the Hand Eczema Severity Index (HECSI).[20] A free calculator is available at www.hecsiscore.com. HECSI involves the severity of six clinical signs (erythema, scaling, infiltration/papulation, vesicles, fissures, and edema) and the involvement areas in both hands (fingertips, fingers, palms, hand dorsi, and wrists), yielding a total score ranging between 0 and 360 points. The final severity is classified according to the score obtained from HECSI (Table 4).[21]

DIFFERENTIAL DIAGNOSIS

Most often, the diagnosis of hand eczema is obvious, and a clinical diagnosis is easily reached. However, additional diagnostic tests such as direct microscopical evaluation of the skin scrapings and histopathological examination may be necessary to distinguish this entity from its differential diagnoses. A complete list of differential diagnoses of hand dermatitis is given in Table 5, and the most common and important disorders mimicking this entity will be discussed in this section. It is essential to keep in mind that up to 20% of patients with hand dermatitis may present with the involvement of feet, and foot involvement is not necessarily caused by endogenous etiological factors.[3,17]

Palmoplantar psoriasis is one of the most important differential diagnoses of hand eczema. Hyperkeratotic hand eczema, especially, may be difficult to distinguish from palmoplantar psoriasis. A thorough medical history, including family history and careful dermatological evaluation of the entire skin for the involvement of the body and other areas, as well as nail findings specific to psoriasis, is necessary. A skin biopsy may be helpful, but histopathological differentiation is also challenging.[22]

TABLE 1: Etiological classification of hand eczema according to ESCD.[17,19]

Etiological Subtypes	Demographic features	Medical history	Clinical presentation	Localization
Irritant contact dermatitis	• The most frequent cause • Most common in females	• Irritant exposure (domestic/occupational) • Frequent handwashing • Occupations at risk: cleaners, healthcare workers, food handlers, hairdressers, construction and metal workers.	• Chronic fissured eczema or pulpitis • Itch and scaling • Pain if fissured	• Extensor and lateral surfaces of fingers • Hand dorsi
Allergic contact dermatitis	• Major cause of hand eczema • Male>female	• Relevant allergen exposure • Positive patch test • Metals, fragrances, preservatives, rubber, glues, dyes, plants	• Erythema, vesicles • Itch • Pain if fissured	• Fingertips • Palms • Spreads from palms to other locations
Atopic hand eczema	• Young age of onset • 1/3 to ½ of patients with chronic hand dermatitis	• Atopic dermatitis	• Absence of vesicles • Features of subacute/ chronic dermatitis with lichenification	• Hand dorsums • Palms • Ventral wrist • Interdigital spaces • Nail involvement • Anatomical snuffbox
Protein contact dermatitis/ contact urticaria		• Relevant protein exposure (latex, animal and vegetable proteins, animal hair) • Immediate skin reaction upon exposure • Prick test/radioallergosorbent test • Patch tests may be negative	• Urticarial rash • Lasting erythema, scaling, infiltration	• Areas of exposure initially • May spread afterwards

ESCD: European Society of Contact Dermatitis.



FIGURE 5: Hyperkeratotic hand dermatitis. Hyperkeratotic plaques and fissures on the palmar area. From the photography archive of Gazi University Faculty of Medicine, Department of Dermatology.

Another important differential diagnosis of hand dermatitis is tinea manuum, a dermatophyte infection of the hands. It is crucial to exclude this entity before prescrib-



FIGURE 6: Acute recurrent vesicular hand eczema (dyshidrotic eczema). Vesicles and erosions on the palmar area and the medial aspect of the hand. From the photography archive of Gazi University Faculty of Medicine, Department of Dermatology.

TABLE 2: Clinical (morphologic) classification of hand eczema according to ESCD.[17,19]

Clinical Subtypes	Demographic features	Medical history	Clinical presentation	Localization
Hyperkeratotic hand eczema	Most common in males	• No apparent endogenous or exogenous cause • Negative patch test	• Hyperkeratosis • Fissures associated with pain • Little itch • Pain if fissured • No vesicles • No inflammation • Erythema, vesicles	• Palms
Acute recurrent vesicular hand eczema		• Recurrent, frequent flares → The presentation is acute, but the entity is considered a chronic eczema • Formerly: Dyshidrotic eczema, pompholyx	• Itch	• Fingers • Palms • Plantar areas may be involved
Nummular hand eczema		• Patchy dermatitis • Dorsal hands • Atopic dermatitis	• Itch • Dry skin • Well-circumscribed plaques with erythema, keratosis, vesicles, exudation • Staphylococcus aureus	• Hand dorsi
Pulpitis	More common in men	• Relevant irritant exposure • Relevant allergen exposure, positive patch test • Fissures • Atopic dermatitis	• Little itch • Atrophic skin • Pain	• Fingertips

ESCD: European Society of Contact Dermatitis.

TABLE 3: Classification of hand eczema according to the source of etiology.

Exogenous	Endogenous
Irritant contact dermatitis	Atopic hand eczema
Allergic contact dermatitis	Hyperkeratotic hand eczema
Protein contact dermatitis/contact urticaria	Acute recurrent vesicular hand eczema

TABLE 4: Classification of hand eczema according to the severity, using HECSI.[21]

HECSI score	Hand Eczema Severity
0	Clear
1-16	Almost clear
17-37	Moderate
38-116	Severe
117-360	Very severe

HECSI: Hand Eczema Severity Index.

TABLE 5: Differential diagnoses of hand eczema.[17]

- Psoriasis
- Dermatophyte infection (tinea manuum)
- Dyshidrosis lamellosa sicca/keratolysis exfoliativa
- Scabies
- Bullous impetigo
- Lichen planus
- Pityriasis rubra pilaris
- Cutaneous T cell lymphoma
- Porphyria cutanea tarda
- Hand-foot-and-mouth disease
- Fixed drug eruption
- Friction blisters
- Chemotherapy-associated hand-foot syndrome
- Palmoplantar keratodermas
- Bowen's disease
- Acrokeratosis paraneoplastica (Bazex syndrome)
- • Secondary syphilis

ing topical corticosteroids for the patient since these medications can lead to a worsening of the dermatophyte infection, an entity called "tinea incognito," which may further blur the clinical picture.[19] Involvement of only one hand may be a valuable clue for diagnosis. Wood's lamp examination, direct microscopic evaluation of the skin scrapings obtained from the edge of the lesion, and, if necessary, mycological culture may help distinguish tinea manuum from hand eczema.

Keratolysis exfoliativa is a palmoplantar dermatosis presenting with air-filled bullae and collarette-type or lamellar desquamation. It has been reported to be caused by premature corneodesmolysis, but the true etiology is unknown.[23]

Scabies usually simultaneously involves other body parts, such as periumbilical and intertriginous areas, but may sometimes mimic hand eczema. It most commonly localizes to the interdigital areas of hands, and dermoscopic examination may help identify the tunnels caused by mites. Intense generalized pruritus that is worsened at night is a useful tip for diagnosis.

Cutaneous T-cell lymphoma, or mycosis fungoides (MF), is another important differential diagnosis. Early MF may present with the involvement of one or both hands, and erythrodermic MF/Sézary syndrome may present with palmoplantar hyperkeratosis. Resistance to treatment of hand dermatitis may suggest MF, and multiple biopsies may be necessary to confirm the diagnosis.[3]

Porphyria cutanea tarda is usually limited to the dorsal aspects of hands (areas of sun exposure). Laboratory workup and histopathological examination will help distinguish this entity from hand eczema upon suspicion.

Hand-foot-mouth disease is an acute viral infection primarily seen in children and young adults. It presents as erythematous papules and vesicles localized to palms, hand dorsi, oral mucosa, perioral, plantar, and perianal areas. It may sometimes be mistaken for hand eczema.[24]

MEDICAL HISTORY AND DIAGNOSIS

The diagnosis of hand eczema depends on medical history including family history, a careful and complete dermatological examination, and additional evaluation such as patch and prick tests, microbiological tests and histopathology.

A careful and thorough medical history is of utmost importance for the diagnosis and classification of hand eczema. Detailed information on the signs and symptoms (presence or absence of itch and pain) and disease course and duration (acute, relapsing, or chronic) should be obtained. Lifestyle factors such as smoking, frequent hand washing, intense domestic work or exposure to allergens and irritants, and occupational and recreational factors (current and previous profession, hobbies, and chemical exposure related to these factors) should also be investigated. The patient should be questioned for the presence of a personal or family history of atopic dermatitis.[3]

The dermatological examination should involve a careful inspection of hands, feet, and the entire skin to exclude differential diagnoses. A dermoscopic evaluation may sometimes help for differential diagnosis.

The gold standard for the diagnosis of contact allergy is epicutaneous patch testing. It should be performed in all patients with chronic hand eczema, suspicion of contact allergy, and those unresponsive to treatment. The patch tests to be applied should be chosen according to the individual's private, recreational, and occupational history. A positive patch test should be evaluated for relevant exposure, and a negative test result does not always exclude the presence of a contact allergy.[17]

For patients describing contact urticaria (i.e., immediate skin reaction following a protein-containing substance such as latex gloves, plant proteins, or animal foods), a skin prick test may be indicated. Repeated exposure to the allergen protein may lead to an eczematous reaction, defined as protein contact dermatitis. In addition to skin prick tests, specific IgE levels may provide additional information on the sensitization profile.[3]

In atopic and nummular hand dermatitis, *Staphylococcus aureus* colonization may be an aggravating or causative factor.[19] Skin swab cultures may reveal information about colonization and secondary infections in such patients. In patients with suspected dermatophyte infections, direct microscopy or fungal cultures of skin scrapings may help confirm or exclude tinea manuum.

Skin biopsies are not necessary for the diagnosis of hand eczema but may be helpful for ruling out differential diagnoses such as psoriasis, lichen planus, or cutaneous T-cell lymphoma.[17]

MANAGEMENT

Several factors including the disease stage, etiology, acuteness, clinical presentation, location, and patient comorbidities, must be taken into account for the effective management of hand eczema. It is crucial to identify any exogenous factors such as allergens, irritants and proteins

TABLE 6: Treatment of hand eczema according to 2022 ESCD guidelines.[17]

		Chronic hand eczema		
	Acute hand eczema	Almost clear	Moderate	Severe/very severe
Patient education	R	R	R	R
Emollients and protective gloves	R	R	R	R
Avoiding allergen exposure	R	R	R	R
Moderate topical corticosteroids	R	R	R	R
Potent topical corticosteroids	R	R	R	R
Systemic corticosteroids	S (short term only)			
Topical tacrolimus		S	S	
Phototherapy			S	
Alitretinoin				R
Cyclosporine				S
Methotrexate				C
Azathioprine				C
Acitretin				C (hyperkeratotic HE)

Abbreviations (As per ESCD 2022 Guidelines):
R: Recommended; S: Suggested; C: May be considered.

contributing to the disease for effective treatment.[17] This section will be based on the 2022 ESCD guidelines. A summary of the treatment modalities for hand eczema can be found in Table 6.

Emollients and moisturizers should be used in all hand eczema patients, to maintain and improve skin barrier function. The choice of emollient can be individualized according to the clinical presentation and patient preferences.[17,25] In addition to the frequent use of moisturizers, patient education, and lifestyle changes, such as avoidance of allergens and irritants, less frequent handwashing, and use of protective gloves lined with cotton gloves for domestic and professional work, are necessary for effective management of hand dermatitis.[19]

Quick recognition and treatment of acute hand eczema are important to prevent chronicity. Topical anti-inflammatory agents to control inflammation and emollients to restore the post-inflammatory skin barrier can be used. The patient should avoid re-exposure to the causative agent for several months after the resolution of acute hand eczema until the complete regeneration of the epidermal barrier.[17]

Topical corticosteroids are the ESCD's recommended first-line treatment for hand eczema. Their long-term intermittent use for maintenance, such as twice or thrice per week may also be considered.[17] Although they are effective, they may cause skin atrophy and impaired repair of the stratum corneum, interfering with recovery in the long term. Combining topical corticosteroids with a calcineurin inhibitor may reduce the adverse effects.[26] In patients unresponsive to or aggravated with topical corticosteroids, corticosteroid-related contact dermatitis should be kept in mind, in which case a different class of steroid preparation should be chosen.

Topical calcineurin inhibitors, especially tacrolimus, which has been shown to induce clinical improvement in hand eczema, can be used as a single agent or in combination with topical corticosteroids in the long-term management of hand eczema.[27] Everolimus cream, however, did not exhibit a signivicant clinical efficacy in chronic hand eczema.[28]

Both narrow-band-UVB and psoralen-UVA (PUVA) phototherapy have been shown to be effective in the treatment of chronic hand dermatitis.[29] PUVA may cause more adverse events, therefore, narrow-band-UVB may be preferrable. UVA1 may be effective in dyshidrotic hand eczema.[30] Overall, ESCD guidelines suggest phototherapy in chronic hand eczema patients refractory to topical corticosteroids.[17]

Systemic corticosteroids are effective; however, since they are associated with long-term adverse effects, their long-term or repeated use should be avoided. The ESCD suggests their use only in acute, severe hand eczema for a short duration (up to three weeks), starting from 0.5 mg/day prednisone and tapering down, to suppress the inflammation until another, slow-acting treatment takes over.[17]

Alitretinoin, an oral retinoid, is the only licensed systemic medication in Europe for the treatment of chronic hand eczema. It is recommended as a second-line medication following topical corticosteroids. Currently unavailable in Türkiye, it can be used in doses of 10-30 mg/daily for a period of 24 weeks. Retreatment is possible in case of relapse, and the treatment can be extended beyond 24 weeks if there is improvement without a complete response. It is more effective for hyperkeratotic hand eczema than acute recurrent vesicular type. The treatment should be stopped if there is no response within three to four months. Similarly to other systemic retinoids, adverse effects include headache (the most common adverse effect), hyperlipidemia, and impaired thyroid function tests. As with all retinoids, alitretinoin is teratogenic and, therefore, requires pregnancy prevention throughout the treatment.[31]

Cyclosporine is indicated for atopic dermatitis in some countries, including Türkiye. It may be beneficial in the treatment of chronic hand eczema.[32,33] In the ESCD Guidelines, it is suggested as a third-line therapy in chronic hand dermatitis patients who are refractory or contraindicated to first- and second-line treatment.[17]

Other systemic treatments that may be considered for severe hand eczema refractory to other treatments are acitretin, azathioprine, and methotrexate, all of which are off-label treatments.[17] Although acitretin has been used in the treatment of hyperkeratotic hand dermatitis, there is limited data on its efficacy. Three studies involving a small number of patients concluded that is is an effective and well-tolerated treatment for refractory hyperkeratotic hand eczema.[34-36] The use of acitretin in this disorder decreased worldwide after the approval of alitretinoin.

Azathioprine drug discontinuation is significantly high, especially during the first three months of treatment, during which the onset of action did not take place.[37] However, it has been found to be somewhat effective for hand eczema and can be used in combination with oral or topical steroids to decrease steroid dependency.[37,38]

There a no randomized controlled trials on the efficacy of methotrexate on hand dermatitis. Two retrospective studies to date have revealed a lower efficacy compared to acitretin, and a low drug survival.[39,40]

Dupilumab is a monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signaling and is indicated in atopic dermatitis. A study including 47 patients with atopic hand eczema showed a favorable HECSI response.[41] Topical delgocitinib, a novel pan-Janus kinase (JAK) inhibitor, has been recently reported to be an effective and well-tolerated agent for the treatment of chronic hand dermatitis, and is currently pending approval in Europe and North America.[42] Gusacitinib is another JAK inhibitor targeting Th1, Th2, Th17, and Th22 cytokine pathways and SYK-mediated IL-17 signaling in keratinocytes.[43] The phase 2 trial of oral gusacitinib for hand eczema has revealed promising results.[44]

CONCLUSION

Hand eczema is a common disorder with economical and psychosocial impact. A thorough medical history together with a careful dermatological examination are essential for the correct classification and determination of the etiology. Patch test is indicated in all hand eczema patients. Patient education is crucial for the prevention and proper management of the disease. New targeted treatment modalities, both systemic and topical, are currently under investigation for hand eczema, and will hopefully lead to better management of the disease in the near future.

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Management of Contact Dermatitis in Atopic Individuals

Atopik Bireylerde Kontakt Dermatit Yönetimi

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ABSTRACT Contact dermatitis is a skin inflammation that can develop due to contact with various substances and significantly affects the quality of life of affected individuals. The prevalence of contact dermatitis in atopic individuals remains unclear due to conflicting data. Although their immunopathogenesis is different, the epidermal barrier impairment in atopic dermatitis and increased exposure to topical products make patients more susceptible to contact dermatitis. The presence of contact dermatitis in atopic dermatitis may exacerbate epidermal barrier dysfunction and increase the severity of the disease. Therefore, it is essential to be aware that contact dermatitis may develop in cases of atopic dermatitis, and understanding its management is crucial. In this article, the management of contact dermatitis in atopic individuals is summarized.

Keywords: Dermatitis, atopic; dermatitis, contact; dermatitis, allergic contact; dermatitis, irritant

ÖZET Kontakt dermatit, çeşitli maddelerle temasa bağlı gelişebilen ve etkilenen bireylerin yaşam kalitesini önemli ölçüde etkileyen bir deri inflamasyonudur. Atopik bireylerde kontakt dermatit prevalansı çelişkili veriler nedeniyle belirsizliğini korumaktadır. İmmunpatogenezlerinin birbirinden farklı olmasına rağmen, atopik dermatitteki epidermal bariyer bozukluğu ve topikal ürünlere artan maruziyet, hastaları kontakt dermatite karşı daha duyarlı hale getirir. Atopik dermatitte kontakt dermatitin mevcudiyeti ise epidermal bariyer fonksiyon bozukluğunu şiddetlendirebilir ve hastalığın şiddetini arttırabilir. Bu nedenle atopik dermatit vakalarında kontakt dermatit gelişebileceğinin farkında olmak ve yönetimini bilmek çok önemlidir. Bu makalede atopik bireylerde kontakt dermatit yönetimi özetlenmiştir.

Anahtar Kelimeler: Dermatit, atopik; dermatit, temas; dermatit, alerjik kontakt; dermatit, irritan

Dermatitis resulting from direct skin exposure to a substance is termed contact dermatitis (CD). This can be either allergic or irritant-induced. Irritant contact dermatitis (ICD) occurs when the contact substance directly damages the skin, representing approximately 80% of occupational contact dermatitis.[1] It is also a prevalent cause of hand eczema.[2] Allergic contact dermatitis (ACD), on the other hand, develops through late-type hypersensitivity. The prevalence of ACD in children and adolescents is approximately 16.5%, with a pooled prevalence of contact allergy at 20.1%.[3,4] Patch testing remains the gold standard for diagnosis.[4]

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease, affecting 15-20% of children and 1-3% of adults.[5] Its pathogenesis involves epidermal barrier dysfunction, genetic factors, immune dysregulation, altered skin microbiome, and environmental triggers. The immune dysregulation in AD is different from ACD; in the past, it was thought that the risk of developing allergic contact dermatitis was low in atopic dermatitis. However, the epidermal barrier dysfunction and the increased exposure to topical products for the treatment of AD may prone individuals to develop contact der-

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matitis. Also, ICD and ACD may contribute to epidermal barrier dysfunction in patients with AD, worsen AD severity, and mimic its clinical presentation.[6] The risk of developing ACD in AD remains controversial, with conflicting data on the allergens involved.

In a retrospective study of 4,509 patients, patch test results of 1743 individuals with "atopic skin diathesis" and 2,165 individuals with "no atopic skin diathesis" were compared. Accordingly, individuals with atopic skin diathesis had at least one more positive patch test reaction to the baseline series than those in the other group (49.1% vs. 38.3%). Atopic skin diathesis was associated with a significantly higher risk of sensitization to methylchloroisothiazolinone/methylisothiazolinone and methylisothiazolinone, thiuram mixture, and nickel, cobalt, and chromium.[7]

Choi YJ et al. evaluated 515 patch test results (53 of them had AD) to determine the characteristics of contact sensitization in ACD patients with a current or past history of AD.[8] The AD group showed decreased positivity for any allergen compared to the non-AD group. The positivity rate for budesonide was significantly higher in the AD group, while the prevalence of positive results for balsam of Peru was higher in the non-AD group.[8] This study supports the view that the prevalence of contact sensitization is reduced in AD patients compared to non-AD patients.

Another study involving 15,737 patients, including 5641 with AD, revealed an increased frequency of ACD in AD patients, than non-AD patients. Increased prevalence of ACD to cosmetics, medicaments, dyes, and foods contacting the skin, but decreased sensitization to metals was observed.[9] This study emphasizes that clinicians must maintain a high index of suspicion for ACD in patients with AD.

The epidemiological, clinical, and allergy profile of 1466 patients with hand eczema was compared with patients with and without AD via Spanish Contact Dermatitis registry data. It was observed that AD patients were younger and their symptoms lasted longer before the test, while non-AD patients were more likely to be exposed to occupational triggers.[10] This suggests that hand eczema can develop in patients with AD even with less trigger exposure and that AD itself predisposes to the development of eczema.

In a study of 112 children with atopic dermatitis and 39 healthy controls, 17% (n=19) of children with atopic dermatitis were sensitized to cosmetic or standard series or both, whereas no child in the control group had a positive patch test (p=0.001). However, the severity of atopy and atopic dermatitis was not found to be a significant risk factor for cutaneous sensitization.[11]

Although a recent meta-analysis showed no significant association between atopic dermatitis and contact sensitization, general population studies have shown increased contact sensitivity in individuals with atopic dermatitis. Clinicians should recommend safe, low-allergenic products to AD patients and consider patch testing when allergic contact dermatitis is suspected in these patients.[12]

Despite contradictory literature data, patch testing may be considered in AD patients under certain circumstances:[13,14]

- AD patients with worsening or more widespread dermatitis,
- Lesion distribution atypical for AD or localized, suggestive of contact dermatitis (e.g. eyelids, head and neck, hands and feet, perioral or periorbital),
- Refractory dermatitis to topical treatment before starting systemic immunosuppressive therapy,
- Worsening of AD with treatment or rapid recurrence with discontinuation of treatment (to see if there is development of ACD to active ingredients or excipients in topical treatments such as corticosteroids or propylene glycol),
- AD patients with widespread nummular lesions.

The management of CD involves identifying the allergen, preventive measures, inflammation treatment, and skin barrier restoration.[15] Treatment of CD is similar in both atopic and non-atopic individuals.

Proper information is crucial for patients to avoid allergens, including common contact allergens such as plant allergens (poison ivy, mango tree, ragweed, etc.), metals, fragrances, acrylates, medicines, and preservatives.[16,17] For example, nickel is found in many objects commonly used in our daily lives, including jewelry, zippers, coins, keys, scissors, children's toys, cell phones, and handheld computers.[18-20] Nickel test kits using dimethylglyoxime can be useful for detecting objects that release nickel; they also do not harm the object being tested. In a study, the nickel spot test had a specificity of 97.5% for detecting released nickel concentrations.[21] Also, some methods to avoid nickel exposure can be explained to the patients. These can include covering a nickel object with a physical barrier such as Nickel Guard or clear nail polish, using duct tape to cover metal parts in contact with the skin, and using iron-on patches on clothing.[22] In addition, chelating creams that inactivate the metal or non-chelating creams that pre-

vent nickel from penetrating the skin can be used as chemical barrier creams.[23,24]

Cosmetics and personal care products contain many chemical ingredients. However, few agents are responsible for most cases of ACD. These include preservatives, excipients, fragrances, glues, sunscreens, and hair dyes.[25-28] AD may require intense skin care and long-term topical treatments. In patients with AD, products with the least additional ingredients should be chosen. The risk of possible sensitization and irritation is high with every topical product applied due to skin barrier impairment in AD. Water contact should be reduced as water can be both an irritant and contribute to skin barrier impairment.

Preventive measures include using pre-work (barrier) creams and post-work (emollient) creams, milder detergents instead of irritating cleaners, and the application of allergen-free emollients (e.g. petrolatum-based emollients) after hand washing.[29,30] Regular use of moisturizers is vital for maintaining skin barrier function.[31]

PHARMACOLOGIC TREATMENT

Topical corticosteroids and topical calcineurin inhibitors, systemic immunosuppressors, and phototherapy are used when necessary and emollients are the mainstay of treatment. The treatment approach varies based on the type and extent of CD.

ACUTE, LOCALIZED CD TREATMENT

First-line treatment for acute, localized CD is topical corticosteroids (TCS). Emollients can be used liberally multiple times a day in addition to topical treatment. High-potency topical corticosteroids for acute CD of the hands, feet, and non-flexural areas (<20 percent of the body surface area) can be applied once or twice daily for two to four weeks or until symptoms improve.[32-36]

Moderate to low potency topical corticosteroids are recommended as initial treatment for acute, localized mild to moderate CD in the face and flexural areas. Topical corticosteroids can be applied once or twice daily for one to two weeks. Afterward, the application frequency can be tapered (e.g., with every other day application) for the following two weeks. In patients requiring long-term, continuous treatment (more than two weeks), topical tacrolimus should be preferred to avoid topical corticosteroid side effects (telangiectasia, skin atrophy, etc.). Tacrolimus 0.1% ointment is applied twice daily until improvement is noted and then tapered. In one study, tacrolimus 0.1% ointment applied twice daily was more effective than placebo in clearing the eruption over eight weeks of continued exposure to the allergen.[37] Pimecrolimus 1% cream does not appear to be effective for ACD.[38]

Calcineurin inhibitors are effective in experimental human models of nickel- and diphenylcyclopropenone-induced allergic contact dermatitis and sodium lauryl sulfate-induced irritant contact dermatitis.[39] Their anti-inflammatory potency reaches the low-to-moderate potency of glucocorticoids.[38,40,41]

ACUTE, EXTENSIVE CD TREATMENT

Prednisone at a dose of 0.5-1 mg/kg per day (maximum 60 mg/day) or an equivalent dose of other systemic corticosteroids for seven days is recommended as first-line treatment for acute disseminated and severe CD (involving >20 percent of total body surface area or the face, hands, feet or genitalia). The dose can then be reduced by 50 percent within 1 week and reduced and discontinued within the next two weeks.

CHRONIC CD TREATMENT

The use of TCS in the treatment of chronic CD should not be longer than 2-4 weeks. Allergen-free moisturizers should be used in addition to other topical treatments in the treatment of CD, especially chronic, lichenified dermatitis.

Intermittent high-potency topical corticosteroids are recommended for long-term control of chronic CD involving the hands, feet, or non-flexural areas. Topical corticosteroids are initially applied once daily for 7-10 days, followed by daily treatment. Topical corticosteroids are applied once daily three times per week on alternate days. In case of relapse, continuous treatment can be switched back. Intermittent and proactive treatment regimens-application, for example, twice a week for up to 6 months-may help to reduce side effects.[39]

For the treatment of chronic CD localized to the face or intertriginous areas and chronic, localized CD refractory to topical corticosteroids, topical tacrolimus 0.1% ointment can be applied once or twice daily to the affected areas until improvement is achieved. In case of relapse, treatment can be restarted.

Phototherapy (bath psoralen plus ultraviolet A photochemotherapy or narrowband ultraviolet B)[42-45] and systemic immunosuppressive agents (Methotrexate, azathioprine, mycophenolate mofetil, and cyclosporine)[46] can be used for chronic CD patients who do not respond to

topical treatments either alone, in combination, or as glucocorticoid-sparing therapeutics.[47] Methotrexate and cyclosporine may be useful in chronic refractory hand eczema.[48,49]

Diets restricting nickel, balsam of Peru, and propylene glycol may be recommended in sensitized patients; however, the benefit of dietary modification in other cases of ACD is controversial.[50]

In conclusion, while the frequency of contact dermatitis in atopic dermatitis remains uncertain, preventive measures, adequate patient information, and vigilant treatment monitoring can reduce its occurrence. Choosing products and treatments with minimal additives is essential to minimize sensitization risk. The treatment approach is consistent for both atopic and non-atopic individuals, focusing on maintaining skin barrier function (Figure 1).

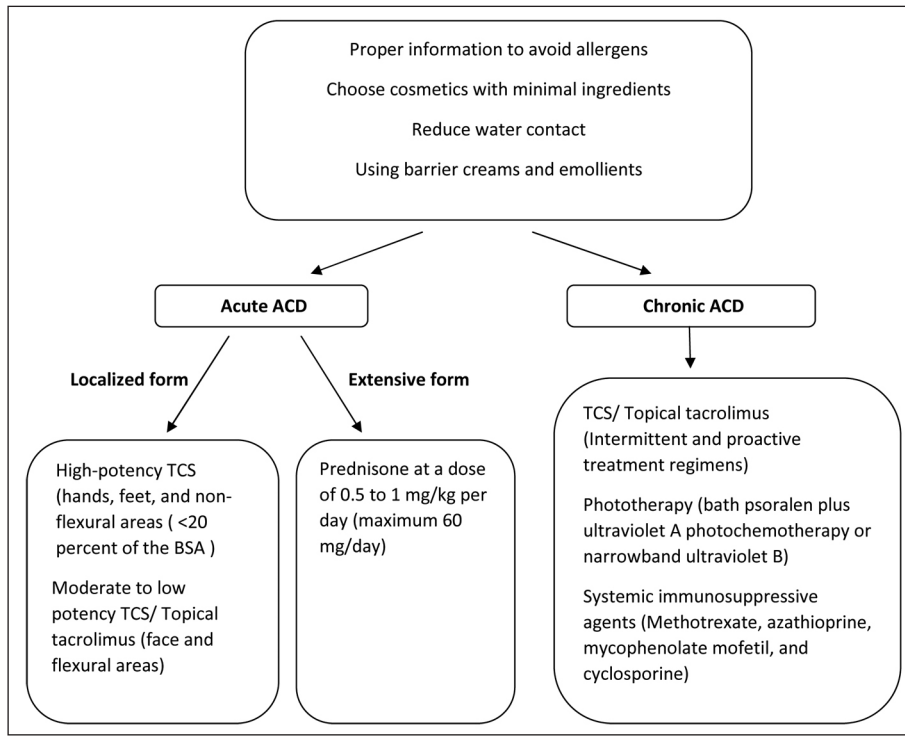


FIGURE 1: Management of contact dermatitis in atopic individuals.
TCS: Topical Corticosteroids; BSA: Body Surface Area.

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Patch Testing

Yama Testi

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ABSTRACT The patch test is an epicutaneous test that shows the presence in tissue of specific T lymphocytes against the contact allergen. It can be used in many indications, especially eczematous allergic contact dermatitis. Standardized allergens can be supplied and tested as standard series or as cosmetic, fragrance, pharmaceutical, and occupational series. In addition, patch tests can be performed with substances with which individuals come into contact in their daily lives, jobs, or hobbies. Patch testing is evaluated according to International Contact Dermatitis Research Group (ICDRG) criteria. Negative, irritant, doubtful positive, or positive reactions should be carefully evaluated. Interpreting positive reactions in the light of patient histories and clinical findings and evaluating their compatibility with the clinical manifestation is the most important step in patch testing.

Keywords: Allergens; patch tests

ÖZET Yama testi kontakt alerjene karşı dokudaki spesifik T lenfosit varlığını gösteren epikutanöz bir testtir. Başta ekzematöz alerjik kontakt dermatit olmak üzere birçok endikasyonda kullanılabilir. Standardize edilmiş alerjenler, standart seri veya kozmetik, koku, ilaç ve çeşitli meslek serileri olarak temin edilebilir ve test edilebilir. Bunun yanı sıra kişilerin günlük yaşamında, mesleksel ya da hobileri nedeniyle temas ettikleri maddeler ile de yama testi yapılabilir. Yama testi, Uluslararası Kontakt Dermatit Araştırma Grubu kriterlerine göre değerlendirilir. Negatif, iritan, şüpheli pozitif ya da pozitif reaksiyonlar dikkatli bir şekilde değerlendirilmelidir. Pozitif reaksiyonların anamnez ve klinik bulgular eşiliğinde yorumlanması ve klinik ile uyumunun değerlendirilmesi yama testinin en önemli basamağıdır.

Anahtar Kelimeler: Alerjenler; yama testleri

Patch testing is a diagnostic test used to evaluate the T lymphocyte-mediated delayed-type cellular hypersensitivity reaction that occurs hours or days after contact with contact allergens with a molecular weight of less than 500 Daltons. In other words, it is an epicutaneous test that indicates the presence in the tissue of specific T lymphocytes against a contact allergen. It was first applied by Josef Jadassohn in 1895 and continues to be frequently employed.[1]

INDICATIONS

The most important indications for the use of the test include non-eczematous contact dermatitis occurring in various clinical manifestations, primarily eczematous-type allergic contact dermatitis (lichenoid, erythema multiforme-like, papular, follicular, pigmented, purpuric, lymphomatoid, or granulomatous), systemic allergic dermatitis, photoallergic contact dermatitis, allergic contact stomatitis, drug eruptions, and atopic dermatitis exacerbated by Type 1 allergens.[2-4]

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TEST MATERIALS, ALLERGENS, AND ADMINISTRATION OF THE TEST

Materials used for patch testing include allergens, the sticking patch test plasters on which these are placed, blotting papers on which liquid allergens are applied, fixing plasters, and skin marking pens or reading templates that help with interpreting the test.[5]

The test is most commonly performed on the upper back, although the upper outer surfaces of the arm can also be used if necessary.[2] In order to perform an accurate evaluation, the skin in the test area must be completely lesion-free, and care must be taken to ensure that the region is clean, dry, and hair-free.

Ready-made test kits are today available for 400-500 allergens. For an allergen to be included in the standard series, the frequency of positive reactions must exceed 0.5-1%, the allergen must be a common one, it should produce reliable and clinically compatible patch test reactions and must not be an irritant/toxic substance, and routine patch testing with this substance should entail no risk of sensitization.[6] Standardized allergens are available as standard, cosmetic, fragrance, pharmaceutical, and various professional series. There are various different standard patch test series, such as the European, International, North American, and Japanese standard series. The European baseline series is frequently used in Türkiye. The number of allergens in the European baseline series rose to 30 following the 2015 revision. In the subsequent revision conducted in 2019, benzocaine was replaced by Kaine mixture III, clioquinol and primin were removed from the series, and 2-hydroxyethyl methacrylate (2-HEMA) and propolis were added.[7] European baseline series allergens are shown in Table 1.

TABLE 1: European baseline series: 2023.

Compound	Concentration % (w/w) in pet except those in aqua[a]
Potassium dichromate	0.5
p-Phenylenediamine	1.0
Thiuram mix	1.0
Neomycin sulphate	20.0
Cobalt chloride	1.0
Caine mix III	10.0
Nickel sulphate	5.0
2-Hydroxyethyl methacrylate	2.0
Colophonium	20.0
Parabens	16.0
N-Isopropyl-N'-phenyl-p-phenylenediamine	0.1
Lanolin (wool alcohols)	30.0
Mercapto mix	2.0
Epoxy resin	1.0
Myroxylon pereirae	25.0
4-tert-Butylphenol formaldehyde resin	1.0
Mercaptobenzothiazole	2.0
Formaldehyde	2.0[a]
Fragrance mix I	8.0
Sesquiterpene lactone mix	0.1
Sodium metabisulfite	1.0
Propolis	10
Methylchloroisothiazolinone (150 ppm) and methylisothiazolinone (50 ppm)	0.02[a]
Budesonide	0.01
Tixocortol pivalate	0.1
Methyldibromo glutaronitrile	0.5
Fragrance mix II	14.0
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	5.0
Methylisothiazolinone	0.20[a]
Benzisothiazolinone	0.1
Textile dye mix	6.6

Standard test antigens are available in plastic syringes in a pure white petrolatum carrier base or in dropper bottles in water-based carriers. It is recommended that allergens be stored in a refrigerator at +4 degrees Centigrade to protect them from heat and light, and horizontally to prevent homogeneous distribution in the carrier.[8] The viability of Vaseline-based products is two years, but 6-9 months for liquid-based allergens. The patches on which the allergens are placed contain 10 chambers in two rows. Different options are available, including plastic or aluminum chambers, self-lids, and drying paper. In the preparation phase, the test patches are first numbered, and the protective part is then opened. If the chambers are not equipped with blotting paper, this is added to the chambers to which liquid allergen will be applied. In order to obtain reliable results, care should be taken not to place too much or too little substance in the test chambers. Vaseline-based allergens are placed in their own chambers (20 mg) such as to fill half the chamber, and liquid-based allergens are placed in their own chambers at a volume of 15-20 microliters with the help of a micropipette immediately before the test.[9-11] The prepared test patches are first attached at the bottom edge, leaving a gap of 2-4 cm on both sides, and then in their entirety, ensuring that no air bubbles remain. A stabilizer patch 2 cm wider than each margin is attached to the test patches. Care should be taken to ensure that the fixative patch has good adhesive and minimal irritant and allergenic properties. The test downtime is 48 hours. However, a period of 24

hours is recommended for children or patients with suspected severe reactions.[12] During this period, the patient is advised not to sweat or bathe, to avoid movements that might loosen the patches, not to sunbathe, and not to scratch the test area. After 48 hours, the patches are removed, and the test areas are marked and numbered with a skin marking pen. Since temporary erythema may occur when the patches are removed, half an hour should be allowed to elapse before the first evaluation. Following the initial evaluation, other assessments can be performed at 72 and 96 hours, or on the seventh day for later reactions.

POINTS TO CONSIDER WHEN APPLYING THE TEST

1- The test area should be completely lesion-free, and patch testing should not be performed in the presence of an active lesion. Two to four weeks should be allowed to elapse after the lesions heal, or 6-8 weeks in the presence of a lesion in the test area.

2- The use of systemic and topical drugs that might suppress the test should be investigated in detail beforehand. Based on clinical experience, patch testing may be considered in patients receiving systemic corticosteroid therapy with prednisolone at a daily equivalent dosage of <20 mg. If possible, treatment with ≥20 mg prednisolone or equivalent corticosteroids daily should be discontinued one week before the patch test.[13] Equivalent periods are 3-4 weeks for immunosuppressive drugs, one week for non-steroidal anti-inflammatory drugs and TNF-α inhibitors, and at least three days for H1 blocker antihistamines. If a topical corticosteroid or calcineurin inhibitor has been applied to the test area for less than one week, the patch test would be better performed after one week, while if it has been applied for ≥1 week, the test should be conducted after 3-4 weeks.[4]

3- If testing is to be performed with substances that the patient uses or comes into contact with, other than standard allergens, the potential irritant/toxic effects of these must be taken into consideration.

4- The most suitable area for patch testing is the upper half of the back. It should be kept in mind that false negative results may occur if different anatomical regions are used due to large numbers of antigens (such as the waist area or inner surface of the forearm).[14]

5- Since contact sensitization can occur at any age, starting from the neonatal period and infancy, patch testing can be performed whenever necessary. However, in the absence of any indication, patch testing should be performed by reducing the concentrations and removing allergens with high sensitization potential, such as p-phenylenediamine, from the series.[15]

6- The T lymphocyte response in individuals aged over 70 is inadequate.[16] In addition, T lymphocyte function and contact sensitization capacity are thought to be impaired in Hodgkin's disease and other neoplasias.[17] The patient's age and accompanying diseases should therefore be taken into consideration before the test.

7- Although there are no data indicating that patch testing has any adverse effect on the fetus, it is still best to avoid it during pregnancy and, if possible, lactation, since small amounts of allergens may be absorbed from the skin.[13]

8- At least 4-6 weeks should be allowed to elapse before testing individuals who are tanned or who sunbathe.[13]

9- Patch testing should not be performed in very hot seasons due to excessive sweating, insufficient occlusion, and the effect of UV rays.

PATCH TESTING WITH NON-STANDARD SUBSTANCES

Patch tests can also be performed on substances with which individuals come into contact with in daily lives, either professionally or via their hobbies. Patch tests with non-standard substances should be prepared and tested at a concentration and pH value that will not cause toxicity or irritation to the skin. Testing should not be done with substances whose contents are unknown. Patch testing can be performed directly using the closed method with cosmetics that do not rinse off and that can remain in contact with the skin for extended periods under normal conditions. In case of rinsed cosmetics, dilution and an open test should be performed first. Drugs that can remain in contact with the skin for extended periods, such as non-rinsed cosmetics are tested directly, while drugs that need to remain in contact with the skin for short periods due to their irritant properties, such as rinsed cosmetics, are tested using the open method. In patch testing with systemic drugs, samples should be prepared in two different base substances, such as water and petroleum jelly.[18] Dilution series are preferred over single-test concentrations. Dilution series of up to 10% with the active ingredient and up to 30% with the commercial preparation are prepared.[19] In patch testing with materials such as fabric, leather, rubber, paper, gloves,

and shoes, 3x3-cm or 5x5-cm samples taken from the inner and outer surfaces of these materials and parts of different structures are wetted and tested on a chamberless patch for at least 72 hours using the closed patch test method.[18] Direct testing should be avoided whenever possible due to the high risk of active sensitization and irritant reactions with plants. In patch testing with technical fluids such as machine oil, mineral oil, boron water, cutting fluid, and cooling fluid, the pH value should be between 5 and 8. Dilution series should be prepared from clean and dirty (used) samples and tested separately.

PATCH TEST EVALUATION AND INTERPRETATION

Patch testing is evaluated according to International Contact Dermatitis Research Group (ICDRG) criteria. Evaluations should be performed in daylight. This will facilitate the assessment of the reaction and the degree thereof, especially since light coming from the side will show the infiltration better. The degree of positivity of the patch test is related to the severity of sensitization. In addition, 1-5% of suspicious patch test reactions, 20-50% of 1+ reactions, 80-90% of ++ positive reactions, and almost all +++ reactions are compatible with the clinical manifestation.[8]

Patch test reactions are evaluated as irritant, suspicious positive (?+), +, ++,+++, and negative reactions according to ICDRG criteria (Table 2).[20]

The degree of reaction may remain the same (plateau) in at least two evaluations, or may initially be negative or suspicious but turn positive in the following days. Alternatively, the initial positivity degree may appear in the form of increasing reactions (crescendo) in the subsequent days. Itching at the test site, extension beyond the test area, an absence of sharp boundaries, and rounding of the corners if square-shaped test chambers are used should be evaluated in favor of a positive reaction. In contrast, a burning sensation, sharply limited reactions that do not exceed the test area, and their gradual disappearance in the following days should suggest an irritant reaction (Table 3).[21] These irritant reactions may occur with standard series allergens such as formaldehyde, fragrance mixtures, thiuram mixtures, lanolin, and cobalt. They are usually evident at the 48th hour and decrease and disappear in the following days. The presence of a reaction only at the edge of the test area, the center being empty, should also be interpreted in favor of an irritant reaction (edge effect).[22] Petechiae purpura may rarely occur as an irritant reaction. Papules/pustules that resemble the follicle openings and direct blisters without vesicle formation should also be considered as irritant reactions.[5]

TABLE 2: The evaluation of patch test reactions according to International Contact Dermatitis Research Group classifications.

Degree	Meaning	Test site reaction
-	Negative	No Reaction
?+	Suspicious positive	Only erythema, no infiltration
+	Positive	Erythema, infiltration ± few papules
++	Positive	Erythema, infiltration, (papule), individual vesicles
+++	Positive	Erythema, infiltration, confluent vesicles/bulla
IR	Irritant reaction	Soap effect, direct bulla, necrosis, pustule etc.

Reactions that occur within the first 10-14 days of the patch test and that increase over the subsequent days should also be considered positive.[23] It also should be remembered that late reactions may occur, especially with corticosteroids and neomycin. Late evaluations are also recommended for substances such as nickel and cobalt and topical medications.[24,25] Rare late positive reactions have also been reported with Peru balsam.[25] In late reactions, late positivity may be expected to occur when the test is repeated. However, in some cases, late-onset reactions may occur as a result of new sensitizations. In this case, an early reaction occurs when the test is repeated. Caution should be exercised in this respect.[23]

INTERPRETATION

Interpreting the test results in the light of histories and clinical findings is the most important step in the patch test. The compatibility of the test results with the clinical manifestation (relevance) must be evaluated, and the presence or absence of allergy must be established. After determining whether the reactions evaluated at the testing sites are false negative or positive and excluding these, a true positive reaction must be related to the current clinical situation in the light of histories and clinical findings, and the symptoms must be explained by this specific sensitization. It is important to investigate factors such as contact with the suspected allergen, the time taken for reactions to appear after contact, the compatibility of the clinical manifestation with the contact area, the onset of symptoms upon contact, and their disappearance when contact is discontinued. Positive reactions that are not compatible with existing clinical findings should not be considered the cause of symptoms.

TABLE 3: Clinical features of positive and irritant patch test reactions.

Irritant reaction	Positive reaction
Erythema without infiltration is observed	Infiltration with erythema is seen
Lesion does not exceed the test area and is sharply limited	Lesion exceeds the test area and is not sharply demarcated
Bulla formation may form directly in the contact area and erosion may develop	Bulla formation may develop from vesicle and then erosion occurs
Follicular pustules may be seen	Pustule may develop from vesicle
Burning sensation is prominent	Reaction remains stable or continues to increase
Reaction tends to decrease with time	Itching symptom is observed
Late onset is not observed	Late onset may be seen

The COADEX coding system is used to determine compliance with the clinical manifestation.[26]

C: Current relevance: The allergen identified as positive in the patch test is compatible with the current clinical manifestation. Allergic contact dermatitis is diagnosed only in this case.

O: Old/past relevance: The allergen identified as positive is compatible with the previous clinical manifestation, symptoms occur with each contact, but it does not explain the current clinical situation. Nickel is the most common allergen responsible for this condition.

A: Active sensitization: occurring on days 10-14 of the patch test. Late positive reactions that occur during the following days should be considered.

D (Doubtful relevance/do not know): The compatibility of the allergen identified as positive on the patch test with the current or past clinical picture is unclear.

E (Exposed): The allergen that elicits a positive reaction in the patch test is unrelated to current and past clinical findings, although sensitization has occurred before. A significant proportion of the positive reactions to Thimerosal are from this group due to its presence in vaccines.

X (cross-reaction): The positive test is due to a cross-reaction with another allergen that is of clinical relevance. Cross-reactivity with other para-amino compounds (such as diaminophenylmethane and benzocaine) may occur in patients who develop allergic contact dermatitis due to sensitization with p-phenylenediamine.

OTHER PATCH TESTS

These include the open (patch) test, multi-repeat open test, strip-patch test, atopy patch test, photopatch test, and intrafocal patch test.

Open testing is preferred for allergens suspected of causing an irritant reaction with prolonged contact with the skin, of leading to contact urticaria, or of causing strong contact sensitization. The inner surface of the forearm is most often used as the test area. The material is applied to or dropped onto an area 5x5 cm in size and left to dry. It is reapplied after 24 hours. The presence of immunological contact urticaria and acute irritant reactions should be checked 20 minutes after the application, and of non-immunological contact urticaria reactions after 60 minutes. The test area is evaluated in terms of delayed-type allergic reaction at the 48th and 96th hours and on day 7.[18]

The multiple-repeat open test is a provocation test employed to distinguish irritant-positive patch test reactions from non-standard substances and to determine the clinical compatibility of such substances. Application to a 5x5 cm area on the elbow joint or outer surface of the upper arm, twice a day for seven days is recommended.[27] The application is halted once the reaction begins. Focal papule formation is considered sufficient for a positive reaction. Since the ICDRG evaluation criteria are not adequate for the evaluation of multiple-repeat open test reactions, new evaluation criteria have been proposed.[28]

In the strip patch test, a thick cellophane tape is applied to the skin and torn away 8-12 times in order to thin the stratum corneum and enhance epidermal penetration. The technique is thus particularly useful in patch testing with hard substances, weak allergens, and periorbital eczema and contact stomatitis agents, and in revealing the agent in cases where a false negative reaction is suspected.[29]

The atopy patch test investigates Type 4 sensitization with type 1 allergens. Its most important indication is atopic dermatitis induced by type 1 allergens (aeroallergens and food allergens). There is no standard test series for atopy patch testing. The allergens to be tested are se-

lected based on the patient's history and clinical examination findings. For the atopy patch test, aeroallergens (house dust mites, pollens, and animal epithelium) must be specially prepared in lyophilized form at a concentration of 200 IR/g and in Vaseline.[30] In atopy patch testing with food, liquids are tested directly, while semi-solid/solid foods are tested by crushing or crumbling them and mixing them with water. Application to the patient's non-lesioned back or upper arm skin during the remission period of atopic dermatitis is recommended. Since the allergens tested are type 1, an open test should first be performed against the risk of early-type reaction. If the test is negative for immunological contact urticaria after 20 minutes and for non-immunological contact urticaria after 45-60 minutes, a classic closed patch test with allergens is performed. In the closed application, an early reaction check should be made at 20 minutes.[31] Since type 1 allergens are large molecules, it is difficult for them to pass through the stratum corneum, and they may cause false negative results, so strip-patch testing can be applied. However, it should not be forgotten that strip patch testing may cause irritant reactions in individuals with atopic dermatitis. As with the classic patch test, the patient is evaluated at 48, 72, and 96 hours and on day 7. The reaction is most evident at the 48th hour and then exhibits a decrescendo course.[32] It is also suggested that the 48th-hour results should be taken into account. Papule formation is prominent in positive reactions and is graded up to ++++.[33]

The photopatch test is used to identify substances that do not exhibit allergenic properties on their own but that become allergenic with UV exposure.[34] Patch testing can be applied in all cases exhibiting photodispersion, especially photoallergic contact dermatitis and photoallergic drug eruptions. The most important photoallergens are chemical UV filters, topical nonsteroidal anti-inflammatory drugs, fragrances, and antiseptics.[35] There are several standard series recommended for photopatch testing. The photopatch test, like the classic patch test, is applied to the back or outer surfaces of the upper arm. All allergens to be tested are applied bilaterally. After 24 hours, the test area to be irradiated is exposed to UVA at a dose appropriate to the patient's skin type (5 J/cm^2 for Fitzpatrick skin type II/10 J/cm^2 for Fitzpatrick skin types III-IV). The test and control areas are covered with an opaque material, after which 48 hours are allowed to elapse. Evaluations are made on the sixth day and, if necessary, on the following days. If a positive reaction to an allergen occurs only at the irradiated test site, the photopatch test is considered positive.[36] If a positive reaction is detected at both the test site and the control site, the patch test is considered positive and the photopatch test negative. If the reaction at the irradiated test site is stronger than that at the control site, this may indicate that both the patch test and the photopatch test are positive, meaning that the same substance is both a contact allergen and a photoallergen.[34]

COMPLICATIONS

The most important complications of the patch test are new sensitization, hot back reaction, exacerbation of old lesions (which may be an indicator of clinical compliance), severe inflammatory reaction, necrosis and scarring, hypo- or hyperpigmentation, staining of the skin and clothes with colored allergens, exacerbation of dermographism, contact urticaria with some allergens, granulomatous reaction, and very rarely secondary infection.[13]

Positivity commencing 10-14 days after the patch test may be a sign of new sensitization or an indicator of late positivity. In the repeat patch test, if a late reaction develops in the first test and an early reaction in the second, new sensitization should be considered. If a late reaction develops in the first test and a late reaction in the second test, then late positivity should be suspected.

Angry back reaction refers to the occurrence of irritant reactions in areas adjacent to strong positive patch test reactions. These are not reproducible, exhibit a regressive (decrescendo) course, and initially appear to constitute a positive reaction. This should be considered in case of a reaction with more than five substances without similar chemical structures.

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Management of Contact Dermatitis

Kontakt Dermatit Yönetimi

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ABSTRACT Contact dermatitis, encompassing irritant and/or allergic types, involves inflammatory reactions upon exposure to irritants and sensitizing agents. The evaluation involves a meticulous medical history and examination, with patch tests serving as the gold standard for diagnosing allergic contact dermatitis. Treatment focuses on allergen identification, and in cases of irritant contact dermatitis, identifying and eliminating specific irritants is essential. Airborne contact dermatitis occurs through exposure to various allergens, especially in occupational settings, necessitating a comprehensive diagnostic approach. Protein contact dermatitis is primarily related with occupational in the food sector, involves skin exposure to proteins. Systemic contact dermatitis is rare and results from systemic exposure to contact allergens, necessitating careful diagnosis and allergen-specific interventions. Photocontact dermatitis, caused by photosensitizing sensitizers and UV radiation, requires identification of specific photoallergens. Overall, managing contact dermatitis involves precise diagnosis, targeted interventions, and patient education, emphasizing the importance of allergen avoidance.

Keywords: Contact, dermatitis; management of disease

ÖZET Kontakt dermatit; irritan ve/veya alerjen maddelere maruz kalma sonucu ortaya çıkan inflamatuar bir dermatozdur. Hastaların değerlendirmesinde ayrıntılı bir anamnez ve muayene şarttır. Alerjik kontakt dermatit için altın standart olan yama testi kullanmaktadır. Airborne kontakt dermatit, özellikle mesleki ortamlarda çeşitli alerjenlere maruz kalma yoluyla ortaya çıkar ve kapsamlı bir tanısal yaklaşım gerektirir. Protein kontakt dermatit, başta gıda sektöründe olmak üzere, yüksek molekül ağırlıklı proteinlere maruz kalma ile ilişkilidir. Sistemik kontakt dermatit nadir görülür ve sistemik maruziyet sonucu ortaya çıkar. Ayırıcı tanıda zorluk oluşturabilir bu nedenle dikkatli tanı ve alerjen spesifik müdahaleler yapılır. Fotokontakt dermatit, fotosensitizan duyarlandırıcılar ile ultraviole ışığın reaksiyonu sonucu ortaya çıkar. Duyarlandırıcıların tanımlanması ve güneşten korunma amaçlanır. Genel olarak, kontakt dermatit yönetimi hedefe yönelik uygulamalar ve hasta eğitimi gerektirir, alerjenlerden kaçınmak ise tüm tiplerde dikkat edilmesi gereken en önemli hususdur.

Anahtar Kelimeler: Kontakt, dermatit; hastalık yönetimi

Eczema represents a frequently observed dermatological condition throughout various populations, and it furthermore stands as the predominant occupational affliction affecting the skin. Eczemas can be categorized using many criteria, such as their morphologies, etiologies, and prevalence rates. Atopic and contact eczemas are distinguished based on the inflammatory response elicited against external and internal agents. Contact dermatitis refers to inflammatory responses that arise when the skin comes into contact with irritants and sensitizing agents. These reactions can be categorized largely as either irritating or allergic in nature. Moreover, there exist several categories of con-

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tact dermatitis, including photoallergic, photoirritant, airborne, protein and systemic contact dermatitis. These subtypes share certain clinical and pathogenetic similarities with the two primary forms, while also exhibiting some variances.[1]

The comprehensive evaluation of contact dermatitis involves obtaining a thorough medical history and conducting a meticulous examination of the patient. Additionally, the use of diagnostic instruments that provide additional support and the careful consideration of potential alternative diagnoses are essential components of the diagnostic process. Once the diagnosis has been established, it is imperative to not only provide medical treatment suggestions but also offer guidance regarding lifestyle modifications and enhancements pertaining to the patient and their environment. The provision of such information is of utmost importance for the recovery and prevention of the disease from reoccurring.[2] This article will examine the therapy of patients with various forms of contact dermatitis within the given setting.

IRRITANT CONTACT DERMATITIS

Irritant contact dermatitis represents the prevailing form of contact dermatitis. This phenomenon is characterized by the absence of involvement of immunological processes and the absence of a prerequisite for prior sensitization. The process encompasses the denaturation of proteins and the infliction of damage to cell membranes as a result of exposure to irritating substances. It occurs when the skin's barrier function is compromised or when its repair capacity is exceeded. The extent of the reaction is contingent upon various elements, including the chemical composition of the irritating material, its concentration, the duration of exposure, and the specific part of the body that is affected. The significance of patient-specific factors, such as the existence of atopy, is also significant. Irritant contact dermatitis can present itself in acute, subacute, and chronic manifestations.[3] After experiencing immediate exposure to an irritating material, it is advisable to identify and eliminate any suspicious substances from the surroundings prior to commencing treatment. Following the incident, it is imperative to cleanse the impacted region meticulously by rinsing it with an ample amount of uncontaminated water.[4] The choice of decontamination solution should be determined by the characteristics of the irritant substance, such as its organic or inorganic origin, acidity or alkalinity, and physical state (liquid, solid, or gaseous). The irritating form of occupational eczemas and hand eczemas, which are frequently observed in individuals engaged in homemaking activities, are prevalent. The principal irritants commonly encountered by individuals working in the metal, construction, chemical, food, cleaning, beauty, and health sectors include organic and inorganic acids, alkalis, disinfectants, organic solvents, metals, plastics, cosmetics, and allergic foods.[5] In certain instances of occupational eczema, the progression of the condition might be sufficiently severe and unresponsive to treatment, necessitating persons to make a career transition.[6] The primary approach to treating contact dermatitis involves the identification of the causative agent and subsequent avoidance of contact with that agent. In instances of irritant contact dermatitis, wherein individuals are regularly exposed to irritants, it is imperative to initially ascertain the specific irritant and furnish guidance regarding vigilance towards other potential agents that may elicit comparable reactions. Given that the sensitivity and prevalence of contact allergies are contingent upon the dosage, it is imperative to maintain low concentrations of allergens in products. The achievement of this objective is facilitated by adherence to guidelines that have been created in accordance with the laws and regulations in various nations.[7] In instances where it is not feasible to avoid exposure to the irritant, it is advisable to employ protective attire such as clothes, face shields, goggles, and gloves that are suitable for the specific situation. When choosing appropriate gloves, it is important to consider the irritants that the patient may be exposed to as well as the prevailing working conditions. In instances where there is an excessive amount of perspiration and maceration, it is advisable to utilize cotton gloves below polymer gloves. The process of occlusion intensifies inflammation through the elevation of pH levels, the promotion of trans epidermal water loss, the enhancement of permeability to low molecular weight irritants, and the augmentation of friction. Hence, it is imperative to exercise meticulous deliberation when selecting gloves, considering the specific irritants to which the patient is exposed and the prevailing working conditions. It is not recommended to reuse single use gloves.[8]

TREATMENT

In patients presenting with active complaints and symptoms, initial treatment options primarily include the use of short-term topical and oral systemic steroids, alongside topical calcineurin inhibitors. Although histamine is not implicated in the pathophysiology of irritant contact dermatitis, oral antihistamines are frequently prescribed in clinical practice to provide symptomatic relief.[9] In instances of inadequate response to topical treatments, nar-

rowband UVB and PUVA therapies may be considered. Evidence from studies has demonstrated their effectiveness, particularly in the management of chronic hyperkeratotic irritant hand eczema.[10]

UV light induces apoptotic cell death in activated T lymphocytes, augments the activity and proliferation of regulatory T cells, and diminishes the reactivity of antigen-presenting cells.[11] In the study by Brass et al., 23 patients with a diagnosis of hand eczema underwent a 3-month treatment regimen comprising PUVA and narrowband UVB therapies, which resulted in significant improvements in quality of life and substantial reductions in both lesions and clinical symptoms.[12] Immunosuppressive drugs are generally not commonly used in the treatment of irritant contact dermatitis because the primary issue is not an immunological reaction but rather a direct irritation response to substances. However, in chronic and severe cases where other treatments have failed, immunosuppressive therapies may rarely be considered. In cases of chronic hand/foot eczema that are resistant to topical treatments and phototherapy, consideration may be given to retinoid therapy (such as alitretinoin or acitretin). Other treatment options include methotrexate, cyclosporine, and azathioprine. For patients who do not respond to these therapies, particularly if hyperhidrosis is involved, botulinum toxin and/or iontophoresis may occasionally provide benefit. In cases where there is no response, it is essential to re-evaluate the diagnosis by performing repeat patch testing and to rule out bacterial or fungal infections through culture and mycological assessment.[13] Novel therapeutic options for irritant contact dermatitis, including JAK inhibitors and dupilumab, are currently being explored. Notably, case reports have been published on the use of the pan-JAK inhibitor delgocitinib and dupilumab in chronic hand eczema. In a study conducted by Worm et al., 91 patients with chronic hand eczema were treated with 30 mg of delgocitinib ointment and a vehicle ointment for 8 weeks. Delgocitinib demonstrated superior treatment efficacy compared to the vehicle.[14] Dupilumab, an approved therapy for atopic dermatitis that inhibits IL-4/13 signaling, was administered to three patients with moderate chronic hand eczema who had previously used topical steroids and two different systemic treatments. The regimen involved a subcutaneous dose of 600 mg on the first day, followed by 300 mg every 14 days for 16 weeks. Significant improvements in lesions and symptoms were observed in these patients.[15]

As a means of providing support, it is recommended that patients get guidance regarding the maintenance of skin cleanliness and the implementation of appropriate care practices. It is recommended that individuals cleanse their skin with a mild soap and lukewarm water, followed by a gentle drying process. It is advisable to refrain from engaging in frequent handwashing. Due to its surfactant properties and ability to create a non-detrimental alkaline milieu on the skin, soap necessitates meticulous removal from interdigital areas and objects such as rings. The process of cleansing can be achieved using soap, with or without the need for water, as well as through the application of skin disinfectants. The efficacy of these procedures varies depending on the composition of the chemicals involved, hence presenting both benefits and drawbacks. A research study conducted in the United States investigated the presence of allergens in medical hand cleansers. The study determined that waterless hand soaps cause fewer allergic reactions compared to water-needed soaps and skin disinfectants.[16] According to the guidelines proposed by the European Contact Dermatitis Society, it is recommended to utilize alcohol-based hand disinfection in instances where hands are not visibly filthy. This recommendation is based on the premise that alcohol is less irritating compared to soap.[17]

Moisturizers are cosmetic chemicals that serve as valuable adjuncts in the treatment of inflammatory skin conditions characterized by reduced skin barrier function. These substances can be categorized into two main groups, namely occlusives and humectants, depending on their respective modes of action. As oily substances, they can form a protective barrier on the skin, hence decreasing the rate of trans epidermal water loss. Moreover, they are favored for their ability to impart a soft and lustrous appearance to the skin. Water-in-oil emulsion or cream formulations are commonly employed for the application of these substances, which are primarily intended for use on skin that is dry or injured. Humectants are compounds characterized by their notable ability to retain water and their ability to undergo dissolution in aqueous solutions. Humectant-based moisturizers are considered appropriate for those with normal or mildly dry skin conditions. These moisturizers are characterized by their ability to be absorbed at a faster rate compared to occlusive moisturizers. As a result, they are preferred by patients due to their cosmetic appeal and contribute to improved patient adherence to skincare routines. In conjunction with the major constituents, moisturizers may incorporate supplementary compounds, including emulsifiers, preservatives, and scents.[18] According to the guidelines provided by the European Contact Dermatitis Society, it is recommended to utilize moisturizers to maintain the integrity of the skin barrier function. How-

ever, it is advised that the selection of these moisturizers should be based on the individual characteristics of the patient.[16] Research on the effectiveness of moisturizers in the treatment of contact dermatitis has produced conflicting findings. While several studies advocate for the utilization of moisturizers in the management and prevention of irritant contact dermatitis, alternative research findings suggest that the application of moisturizers on unaffected skin may heighten its susceptibility to irritants or allergens.[19,20] The observed disparity is believed to be ascribed to the active and auxiliary components present in the moisturizer, in addition to factors such as the place of application, duration of use, and quantity used.[21]

ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis is classified as a type 4 delayed hypersensitivity reaction, which manifests when the skin is re-exposed to a chemical that had previously sensitized the individual. The sensitization cascade is initiated subsequent to the initial exposure to the allergenic substance. Upon many instances of exposure, an immune response mediated by T-cells is elicited, resulting in the emergence of inflammatory signs. In the present era, there has been a notable rise in both the quantity of allergenic chemicals and the prevalence of allergic diseases. The sources of allergens exhibit regional variability, encompassing industrial, occupational, cosmetic goods, and cleaning agents, among others.[1] The clinical importance of allergenic chemicals has the potential to vary over time. In preceding years, nickel, neomycin, cobalt, formaldehyde, and bacitracin were more frequently observed. Based on the findings of the patch test conducted by the North American Contact Dermatitis Group throughout the period of 2019-2020, involving a total of 4121 patients, it was seen that nickel continued to be the predominant allergen. Following that, the compounds methylisothiazolinone, fragrance mix, linalool hydroperoxides, and benzisothiazolinone were found.[22] Nickel sensitivity is a commonly encountered condition, often manifesting through exposure to earrings in women and through occupational and hobby-related activities in males. Moreover, nickel is present in a diverse range of items, including coins, keys, eyeglass frames, watchbands, and zippers. The incidence of nickel sensitivity exhibits a tendency to escalate during the summer season as a result of the solubilization of the metal via perspiration in elevated temperatures.[23] Methylisothiazolinone and benzisothiazolinone are commonly employed as preservatives in cosmetic, culinary, and industrial applications with the purpose of inhibiting microbial deterioration and prolonging the duration of product viability.[24] In contrast, linalool hydroperoxides are frequently seen within the cosmetic business, where they serve as constituents of fragrances. These compounds have the potential to be synthesized artificially or extracted from a variety of botanical sources, including mint, cinnamon, and birch.[25]

Allergic and irritant contact dermatitis exhibit distinct clinical characteristics in their acute, subacute, and chronic manifestations. Nevertheless, relying solely on historical accounts and clinical observations may not always be adequate for the purposes of diagnosing a condition and determining the specific allergen involved. The patch test, which is considered the gold standard test for diagnosing allergic contact dermatitis, can be utilized in such instances. Over the course of several years, this method for identifying allergies has been universally accepted. Both American and European groups offer standard or extended series, along with specialized panels tailored to specific occupational groups. A positive reaction detected in the patch test does not necessarily indicate that the clinical presentation is a result of exposure to that antigen. The identified positives may be indicative of sensitization from past exposures that the patient may no longer encounter. In instances where the patch test yields positive results, it is imperative to furnish the patient with both oral and written documentation pertaining to the specific drugs to which they exhibit sensitivity. It is advisable to promote the practice of reading product labels among patients in order to mitigate exposure to allergenic substances.[26]

TREATMENT

The paramount measure in the therapy process involves enhancing the patient's awareness and ceasing their contact with the allergenic substance. In addition to the treatment options for irritant contact dermatitis, topical magistral preparations, topical corticosteroids, and calcineurin inhibitors, PDE4 inhibitors, short-term systemic steroids, antihistamines, acitretin, methotrexate, cyclosporin, mycophenolate can be used in the treatment of allergic contact dermatitis. Some patients may benefit from phototherapy using UVB or PUVA.[27] In a 12-day study involving 66 patients conducted by Queille-Roussel et al., the efficacy of pimecrolimus cream was found to be superior to that of both betamethasone-17-valerate and the vehicle cream.[28] The efficacy of immunomodulatory drugs is limited, with a lack of extensive and comprehensive studies available. Although some patients have experienced benefits, the effectiveness varies depending on the characteristics of the disease and the response to treatment. TNF-alpha

inhibitors are also agents that can be used in treatment; however, there is limited data available in the literature.[29,30] In recent years, biologic therapies that have become increasingly common for many diseases have also shown effectiveness in allergic contact dermatitis. In resistant cases where avoiding triggers is not possible or when a trigger cannot be identified despite patch testing, IL-4 receptor inhibitors such as Dupilumab and Janus Kinase Inhibitors may be used.[31,32] The literature includes case reports demonstrating the effective management of severe chromium-induced allergic contact dermatitis affecting the hands, face, and neck in a 55-year-old cement worker using dupilumab.[33]

Ch'en et al. have documented the successful management of concomitant allergic contact dermatitis lesions in two patients with psoriasis through the administration of upadacitinib.[34]

AIRBORNE CONTACT DERMATITIS

Airborne contact dermatitis is a form of inflammatory dermatitis that exhibits clinical similarities to both allergic and irritant contact dermatitis. It occurs when the skin's exposed regions, including the face, neck, hands, arms, and legs, come into contact with various allergens, such as airborne dust, pollen, organic and inorganic chemicals, as well as volatile substances.[1] Occupational factors are the primary cause of this dermatitis, with plants being recognized as the predominant allergens in most cases. Various substances commonly encountered in the natural environment, including wood, rubber, resin, wool, grain dust, specific tree species, animal fur, as well as cement, certain medications (such as insecticides and medical drugs), perfumes, and room and hair sprays, have the potential to elicit allergic reactions. Sensitization can manifest either through initial exposure to the allergen via airborne means or as a consequence of interaction with an already sensitized substance through the atmosphere.[35] There is a frequent misidentification of airborne contact dermatitis with photoallergic/photoirritant contact dermatitis and polymorphic light reaction. The process of diagnosing a condition involves a comprehensive analysis of the patient's medical history and careful evaluation of their clinical presentation. In some cases, patch testing may also be employed as a diagnostic tool.

TREATMENT

The primary approach to managing treatment for contact dermatitis, as is the case with other instances of this condition, revolves around the avoidance and protection against the allergen. The prioritization of determining the occupational etiology is essential. Patch or photopatch testing is a diagnostic procedure that can be utilized to evaluate potentially problematic chemicals. It is recommended to refrain from engaging in outdoor activities, particularly when the causative agent is of botanical origin, particularly during periods characterized by elevated amounts of pollen, such as the spring and summer seasons, and in specific geographical regions during the autumn months. When engaging in outdoor activities, it is important to consider several precautions to ensure personal safety and well-being. These precautions include measures such as sun protection, the use of masks, and safeguarding exposed regions using hats, umbrellas, gloves, and long clothes. It is recommended to engage in regular maintenance activities such as cleaning personal goods, linens, pillows, and bedspreads, as well as frequently utilizing a vacuum cleaner. Additionally, it is advised to refrain from keeping plants indoors and to diligently remove weeds from the garden. Frequent bathing has been found to be an efficacious approach for the removal of proteins or irritating compounds that have been absorbed via the skin. The application of a barrier cream following each bathing session is crucial to effectively inhibit the permeation of antigens through the skin. In situations when it is not possible to avoid exposure to the allergen and individuals experience persistent and severe lesions, they may be compelled to relocate from the impacted region or alter their occupation.[36,37] "Short-term topical and systemic corticosteroids may be utilized in the management of lesions. However, long-term treatment may necessitate the initiation of systemic immunosuppressive therapy. In this context, methotrexate, azathioprine, cyclosporine, and mycophenolate may be employed. Recently, dupilumab and Janus kinase inhibitors have also been added to the treatment repertoire.[38] Successful cases have been reported with the use of tofacitinib and abrocitinib. Khurana et al. reported improvement in a resistant case of airborne contact dermatitis associated with the Parthenium plant found in India, following treatment with tofacitinib.[39]

PROTEIN CONTACT DERMATITIS

Protein contact dermatitis is a form of contact dermatitis that is predominantly reported as an occupational dermatosis among those employed in the food sector. Lesions are predominantly observed on the hands and arms, exhibiting limited propensity for dissemination to other anatomical regions. This dermatitis arises as a result of the skin's contact with proteins of substantial molecular size.[1]

Protein penetration is more prone to occur in instances when the integrity of the dermoepidermal barrier is disrupted, particularly among those with a previous medical record of atopic or contact dermatitis. The precise etiology of this particular variant of contact dermatitis remains incompletely elucidated; nevertheless, current understanding posits the involvement of both type 1 and type 4 immunological reactions. Protein contact dermatitis, a well-documented condition, is attributed to the exposure of individuals to allergens. These allergens can be categorized into two main groups: plant-derived proteins and animal-derived proteins. The allergenicity of latex, a widely recognized plant-derived protein, has been observed to elicit both type 1 and type 4 hypersensitivity reactions. From a clinical standpoint, it is worth noting that the prevailing manifestation typically involves the recurrence of subacute or chronic hand eczema subsequent to contact with the allergen. However, it is important to acknowledge that distinguishing between this condition and contact dermatitis can be arduous due to the presence of urticarial lesions during the initial time following contact. In instances where protein contact dermatitis is suspected, it is common practice to administer both patch and prick testing. In most situations, patch tests yield negative results, but prick tests exhibit greater sensitivity.[40] It is a commonly observed phenomenon that lesions tend to cure during periods of holidays or when individuals take breaks from work. However, it is customary for dermatitis to immediately rebound following the resumption of job activities.

TREATMENT

The foremost objective in preventing the occurrence of lesions, similar to other types of dermatitis, is to avoid any contact with the allergen. Regrettably, complete avoidance may not be practically achievable, particularly in occupational scenarios. As a precautionary measure, it is advisable to refrain from using rubber and latex gloves that contain latex, and instead opt for the usage of plastic gloves. It is recommended to rapidly wash hands after coming into contact with substances that raise suspicion, and if feasible, to also moisturize them.[41]

SYSTEMIC CONTACT DERMATITIS

Systemic contact dermatitis is an infrequent inflammatory skin condition that manifests in persons who already have a predisposition to hypersensitivity reactions of type 4 and type 3. This dermatosis arises subsequent to the administration of a contact allergen by systemic means. The condition exhibits a diverse range of clinical presentations that may become evident within a short period following exposure. The presence of lesions is particularly noticeable in the area where first sensitization occurs, although they have the potential to extend to other regions. The allergen can enter the body through multiple routes, with oral intake being the predominant mode of entry.[42] Primary sources encompass many substances such as meals, metals, and medications, which get access to the systemic circulation via these specific entry channels. Oral ingestion of several food allergies commonly includes Peru balsam, garlic, propolis, composites, cashew nuts, raw shiitake mushrooms, propylene glycol, sorbic acid/sorbates, and aspartame. Prominent metallic elements encompass nickel, cobalt, chromium, gold, mercury, and zinc. Numerous pharmaceutical substances, including antibiotics, antifungals, anesthetics, corticosteroids, non-steroidal anti-inflammatory medications, biological agents, antineoplastic therapies, and radiocontrast agents, have the potential to elicit allergic reactions within the drug classification. Topically applied drugs can cause a reaction either through cutaneous absorption or via systemic agents that cross-react. Occasionally, a chemical response may transpire when the metallic component within the composition of a consumable item or pharmaceutical medicine interacts with its surroundings.[43] The diagnostic process entails the utilization of patch tests and oral provocation tests. Physicians should prioritize considering systemic contact dermatitis as the initial diagnosis in cases of dermatitis that are resistant, broad, or recurrent, due to its capacity to imitate numerous other dermatological disorders. In general, the confirmation of a diagnosis often involves the reintroduction of the allergen to the patient through non-cutaneous means.

TREATMENT

After the identification of allergies, a crucial initial step in treatment is providing patients with education regarding the several pathways by which they may come into systemic contact with these allergens[42]. One illustrative instance is the prevalence of nickel as the primary allergen in cases of allergic contact dermatitis. Nickel is commonly seen in a variety of consumer goods, including cosmetic products, jewelry, and technology devices. The concentration of nickel in various dietary items might exhibit variability based on the quantity present. Leafy green vegetables, carrots, tea, figs, and mushrooms are characterized by relatively low nickel content, whereas nuts (including almonds, walnuts, and peanuts), chocolate, oats, lentils, and chickpeas, which fall under the category of legumes, exhibit elevated levels of nickel.[44] The recommendation of a nickel-restricted diet for all patients with localized contact dermatitis to nickel is a topic of debate.

This is primarily due to several factors, including the fact that not every patient with localized contact dermatitis will develop systemic contact dermatitis. Additionally, there is limited evidence to support the notion that all patients will experience lesion improvement following a nickel-free diet. Furthermore, daily nickel intake can vary among different populations and even within an individual on different days and during different seasons.[45] Nevertheless, research has indicated that adhering to a dietary regimen with reduced nickel content, particularly by avoiding foods high in nickel, can result in amelioration of lesions and symptoms experienced by patients.[46] Patients may receive recommendations to choose for distilled, boiled, or bottled water as part of their daily routine. It is advisable to refrain from utilizing stainless steel utensils during the cooking process, particularly while preparing acidic dishes, as there is a potential risk of nickel release. Additional suggestions encompass refraining from the utilization of multivitamins containing nickel and, in the absence of any contraindications, including vitamin C supplements that mitigate nickel absorption when co-administered.[47] Oral hyposensitization can be utilized as a treatment modality for individuals exhibiting symptoms of both cutaneous and extracutaneous nature, specifically in the context of systemic nickel allergy syndrome, with the aim of desensitizing the individual to nickel. The process of hyposensitization has been found to enhance the tolerance levels of individuals who face challenges in their everyday activities. In a study conducted by Rizzi et al., the assessment of quality of life was undertaken before and after a one-year period of oral nickel hyposensitization involving a cohort of 52 patients. The findings revealed a noteworthy enhancement in the quality of life among the patients subsequent to the treatment, as compared to their pre-treatment condition.[48] Cobalt is an elemental constituent frequently encountered in conjunction with nickel. The presence of cobalt can be observed in various items such as jewelry, food products, equipment involving metal, and B12 vitamin supplements, namely those containing cyanocobalamin or hydroxocobalamin.[49] In addition to nickel, mercury, and zinc elements, the utilization of these elements in dental clinics for operations such as fillings has the potential to induce systemic symptoms. To mitigate potential medical issues associated with dental procedures, it is imperative to conduct a comprehensive assessment of both the patient's medical and dental histories. It is recommended to conduct patch testing in patients who are suspected of exhibiting allergic reactions to dental products. In the event that patients exhibit allergies, it is advisable to eliminate items containing these substances to the greatest extent feasible.[50,51]

PHOTOCONTACT DERMATITIS

Photocontact dermatitis is a skin disorder that arises due to the interaction between a photosensitizing sensitizer applied topically and ultraviolet (UV) radiation or sunshine. When it occurs in the absence of preceding sensitization and is caused by direct cellular damage through non-immunological mechanisms, it is classified as photoirritant. When an individual experiences a type 4 delayed hypersensitivity reaction that necessitates prior sensitization, it is categorized as photoallergic.[1] Photoirritant contact dermatitis is a more prevalent occurrence compared to photoallergic dermatitis, often characterized by a greater intensity of exposure over shorter durations. The comprehensive evaluation of photocontact dermatitis involves thorough inquiry into the patient's medical history, occupational background, recreational activities, cosmetic regimen, and the specific products that come into direct contact with the skin. In conjunction with the patient's medical background, photopatch testing serves as a diagnostic tool for the identification of the specific allergen responsible for photoallergic dermatitis.[52] The primary causative agents of photoirritant dermatitis encompass furocoumarins (specifically psoralens), various botanical sources such as lemon, carrot, bergamot, celery, fennel, dill, fig, and carrot, as well as pharmaceuticals, dyes, and tar. Photoallergic dermatitis is frequently caused by topical NSAIDs, sunscreens, and scent compounds.[53]

TREATMENT

The primary tenet in the management of this condition is to refrain from exposure to the presumed photoallergens that precipitate the adverse reaction. It is advisable to employ protective garments and accessories, such as long-sleeved shirts, caps, and umbrellas, which serve to limit or diminish ultraviolet exposure. Additionally, the application of physical sunscreens is encouraged. The identification of the precise photoallergen is of most importance in order to effectively prevent the occurrence of further episodes. In the event that a photoallergen is detected during photopatch testing, it is imperative to provide the patient with appropriate notification, particularly with respect to potential cross-reactive agents.[54] Patients should be informed that UV-A rays can penetrate through windows in homes and vehicles. Additionally, when prescribing photosensitizing medications, it is crucial to educate patients about the associated risks and to advise them to use appropriate sun protectiion.[55] In mild cases, inflammation can be managed with topical corticosteroids, calcineurin inhibitors, or short-term systemic steroids. In severe and resistant cases, the

treatment approach is similar to that of allergic contact dermatitis.[11]

In conclusion, management of contact dermatitis should be tailored for each patient. Causative agents, occupational exposures, seasonal changes, climate, specific factors in patient such age, concomitant diseases, daily activities are important for management. Optimal management of contact dermatitis comes with decreased drug use and increase quality of life. he subtypes of contact dermatitis and treatment strategies are summarized in Table 1.

TABLE 1: Treatment strategies for subtypes of contact dermatitis.

Subtypes	Treatment Strategies
Irritant Contact Dermatitis	Avoidance of irritants, Skin care and barrier protection (emollients and moisturizers), Environmental control and protective equipment, Occupational change or relocation, Medical management (topical or systemic corticosteroids and calcineurin inhibitors, methotrexate, azathioprine, cyclosporine, mycophenolate, dupilumab and Janus kinase inhibitors)
Allergic Contact Dermatitis	Avoidance of allergens, Barrier creams and moisturizers Medical management (Topical magistral preparations, topical corticosteroids, and calcineurin inhibitors, PDE4 inhibitors, short-term systemic steroids, antihistamines acitretin, methotrexate, cyclosporin, mycophenolate, phototherapy, TNF-alpha inhibitors, dupilumab, JAK inhibitors)
Airborne Contact Dermatitis	Avoidance and protection against the allergen, Avoidance of outdoor activities, Personal safety precautions (sun protection, the use of masks, hats, umbrellas, gloves, and long clothing, frequent bathing), Indoor plant and weed management, Medical management (topical or systemic corticosteroids and calcineurin inhibitors, methotrexate, azathioprine, cyclosporine, mycophenolate, dupilumab and Janus kinase inhibitors)
Protein Contact Dermatitis	Avoidance of allergen, Minimization of direct hand contact, Use of protective gloves (avoid using latex gloves and instead opt for plastic gloves), Medical management (topical or systemic corticosteroids and calcineurin inhibitors), Skin care (emollients and moisturizers for support skin barrier)
Systemic Contact Dermatitis	Identification and avoidance of the allergen, Patient education, Oral hyposensitization, Skin care and protection (Protective Clothing, barrier cream, moisturizers) Medical management (topical or systemic corticosteroids and calcineurin inhibitors)
Photocontact Dermatitis	Avoidance of photoallergens, Limitation of UV exposure, Use of Ssnscreen, Patient education, Medical management (topical or systemic corticosteroids and calcineurin inhibitors are primarily employed. For resistant cases, the treatment approach resembles that of allergic contact dermatitis)

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