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High ferritin levels are associated with hepatosplenic candidiasis in hematopoietic stem cell transplant candidates

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SUMMARY

Objectives: Invasive fungal infections (IFI) are a significant cause of morbidity and mortality in hematopoietic stem cell transplant (HSCT) recipients. Hepatosplenic candidiasis (HSC) is defined as a distinct form of invasive candidiasis, with liver, spleen, and kidney involvement, in patients with hematological disorders.
Methods: The charts of 255 patients (male/female 168/87; median age 35 (range 16–71) years) who were evaluated pre-HSCT at the Gazi University Hospital Stem Cell Transplantation Unit between 2003 and 2008, were retrospectively reviewed.
Results: HSC, which was demonstrated in six (2.3%) patients, was found to be more common in allogeneic HSCT recipients than in autologous HSCT recipients and in patients who had received two or more previous chemotherapy courses than in patients who had received fewer than two ($p > 0.05$). Patients with HSC tended to have a worse performance status than patients without HSC according to the World Health Organization ($p = 0.001$) and Karnofsky scale ($p = 0.007$). Pre-transplantation ferritin ($p = 0.008$) and acute phase reactant levels, including erythrocyte sedimentation rate ($p = 0.025$) and C-reactive protein ($p = 0.007$), were significantly higher in patients with HSC than in patients without HSC.
Conclusions: This study shows the predictive role of pre-transplantation ferritin levels in selecting a subset of patients at increased risk for HSC. Pre-transplantation risk assessment and targeted strategies might lower the morbidity and mortality of IFI in HSCT recipients.
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1. Introduction

Invasive fungal infections (IFI) are a significant cause of morbidity and mortality in hematopoietic stem cell transplant (HSCT) recipients.[1] Hepatosplenic candidiasis (HSC), or chronic disseminated candidiasis, is a serious clinicopathological entity with predominant involvement of the liver, spleen and occasionally kidneys by candidal microabscesses.[2] The reported frequency of HSC ranges between 3% and 29%.[3–7] Anttila et al. reported HSC in 6.8% of 562 acute leukemia patients.[4] In an autopsy series, HSC was demonstrated in 67 (9%) of 731 HSCT recipients.[6]

HSC is more common in patients who receive highly mucotoxic chemotherapeutic agents.[3] The typical clinical findings of HSC are persistent fever, abdominal pain, nausea, vomiting, and elevated serum alkaline phosphatase levels.[8] The increased frequency of HSC in immunosuppressed patients may be attributed to the increased availability of various diagnostic procedures, such as magnetic resonance imaging (MRI) and histopathologic examination.[4] Although Candida may not be detected by blood cultures, different organs such as liver, spleen, kidney, lung, skin, and bone may become seeded by Candida during the neutropenic period.[3,9] *Candida* species are the most commonly isolated fungal pathogens in immunosuppressed patients. The accurate diagnosis of HSC is based on tissue biopsy showing budding yeast/pseudohyphae or positive blood cultures for Candida in the presence of radiological evidence. The difficulty in early diagnosis and lack of effective antifungal prophylaxis are claimed to be the major causes of poor outcome.[2]

Iron overload (IO) has a significant role in the pathogenesis of various infections through free radical-induced tissue damage. Serum ferritin levels and transferrin saturation (TS) are indicated as predictors of body iron stores.[9,10]

We planned this retrospective study to determine clinical and biological risk factors, including iron parameters, in the pathogenesis of HSC in HSCT candidates.

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Table 1
Characteristics of patients with hepatosplenic candidiasis

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (years)/gender	33/F	24/F	25/F	33/M	52/M	29/M
Diagnosis	NHL	MDS	HD	AML	AML	AML
Transplant type	Autologous	Allogeneic	–	–	Allogeneic	Allogeneic
Conditioning regimen	BEAM	BuCy	–	–	TBIFlu	BuCy
GVHD prophylaxis	–	Cyclosporin A, methotrexate	–	–	Cyclosporin A, methotrexate	Cyclosporin A, methotrexate
Antifungal prophylaxis	Fluconazole 100 mg/day	Fluconazole 100 mg/day	–	–	Fluconazole 100 mg/day	Fluconazole 100 mg/day
Pre-transplant ferritin (ng/ml)	9066.1	1842.7	991.7	3485	956.6	2000
Pre-transplant ALP (U/l)	148	81	158	54	95	NA
HSC time	Day 20	Pre-transplant	Pre-transplant	Pre-transplant	Day 208	Day 20
HSC type	Probable	Probable	Proven	Probable	Probable	Probable
Infection site	Hepatosplenic	Splenorenal	Hepatosplenic	Hepatosplenic	Hepatosplenic	Hepatosplenic
Diagnostic procedure	USG/CT	CT	Tissue biopsy	CT	MRI	MRI
Concomitant fungal infection	PFI	–	–	PFI	PFI	–
Current status	Dead	Dead	Dead	Alive	Alive	Dead
Cause of mortality	Progressive disease	Infection	Infection	–	–	Infection

ALP, alkaline phosphatase; ; AML, acute myelogenous leukemia; BEAM, carmustine, etoposide, cytosine arabinoside, melphalan; Bu, busulfan; CT, computerized tomography; Cy, cyclophosphamide; F, female; Flu, fludarabine; GVHD, graft-versus-host disease; HD, Hodgkin's disease; HSC, hepatosplenic candidiasis; M, male; MDS, myelodysplastic syndromes; MRI, magnetic resonance imaging; NHL, non-Hodgkin's lymphoma; PFI, pulmonary fungal infection; USG, ultrasonography; TBI, total body irradiation.

2. Patients and methods

The charts of 255 patients (male/female 168/87; median age 35 (range 16–71) years) who were referred to the Gazi University Hospital Stem Cell Transplantation Unit between 2003 and 2008 for HSCT, were retrospectively reviewed. Medical data including patient characteristics, type and treatment of underlying disorder, risk factors such as diabetes mellitus, steroid administration, neutropenia and immunosuppressive therapy, liver function tests, transfusion burden, and iron status were evaluated.

Proven HSC was defined as multifocal lesions in the liver and/or spleen on imaging techniques and a specific diagnosis of fungal infection established by the examination of deep-tissue biopsy specimens or blood cultures. Infection was designated as probable when multifocal lesions were shown in the liver and/or spleen by imaging techniques in the absence of microbiological and histopathological evidence.[11] Patients who had a fungal infection without any evidence of liver or spleen involvement were not considered to have HSC. At least two sets of blood cultures were obtained at the onset of fever and were repeated in cases of persistent fever. Liver tissue was obtained by ultrasound-guided needle biopsy from selected patients. All biopsy specimens were subjected to culture, pathological examination, and staining. Imaging studies including computed tomography (CT), ultrasonography, and magnetic resonance imaging (MRI) were performed for each patient.

3. Statistical analysis

Continuous variables in two groups were compared using the Mann–Whitney U-test. Categorical variables were compared using the Chi-square test. A p-value of <0.05 was accepted as statistically significant. The calculations were carried out using SPSS 11.5 (SPSS Inc., Chicago, IL, USA).

4. Results

HSC was demonstrated in six (2.3%) of 255 patients in our study cohort. Five patients had probable and one patient had proven HSC. HSC was more common in allogeneic HSCT recipients than autologous HSCT recipients and in patients who had received two or more previous chemotherapy courses than in patients who had received fewer than two ($p > 0.05$). Patients with HSC tended to have a worse pre-HSCT performance status (PS) than patients without HSC according to the World Health Organization ($p = 0.001$) and Karnofsky scale ($p = 0.007$). Patient characteristics are summarized in Table 1.

Pre-transplantation ferritin levels were significantly higher in patients with HSC than in patients without HSC (1921.3 (956–9066) ng/ml vs. 540 (2.1–7204) ng/ml; $p = 0.008$). Pre-transplantation TS levels were found to be higher in patients with HSC than in patients without HSC (69% (58–80) vs. 22% (6–205)), without statistical significance ($p > 0.05$). Pre-transplantation acute phase reactants, including erythrocyte sedimentation rate (95.0 (80–111) mm/h vs. 42.9 (0–160) mm/h; $p = 0.025$) and C-reactive protein (132.0 (50–252) g/l vs. 13.8 (0–243) g/l; $p = 0.007$), were significantly higher, while albumin levels were lower (3.6 (3.1–4.1) g/dl vs. 4.5 (2.3–5.8) g/dl; $p = 0.022$), in patients with HSC when compared to patients without HSC. Pre-transplantation data categorized according to HSC status are shown in Table 2.

The overall mortality rate was found to be 66.7% in the HSC group. The cause of mortality was progressive disease in one patient and infection in three patients. Univariate and multivariate analysis could not be performed due to the small number of patients with HSC.

Table 2
Comparison of patient pre-HSCT parameters based on hepatosplenic candidiasis status

	HSC-negative	HSC-positive	p-Value
Age (years)	36 (16–71)	31 (24–52)	>0.05
Gender (F/M)	84/165	3/3	>0.05
Ferritin (ng/ml)	540 (2.1–7204)	1921.3 (956–9066)	0.008
TS (%)	22 (6–205)	69 (58–80)	>0.05
AST (U/l)	19 (4–117)	13 (9–17)	>0.05
ALT (U/l)	21.5 (4–221)	19.5 (18–21)	>0.05
GGT (U/l)	27 (22–485)	31.5 (28–35)	>0.05
ALP (U/l)	100 (12–367)	88 (81–95)	>0.05
TPN (+/−)	94/155	2/4	>0.05
ESR (mm/h)	42.9 (0–160)	95.0 (80–111)	0.025
CRP (g/l)	13.8 (0–243)	132.0 (50–252)	0.007
Albumin (g/dl)	4.5 (2.3–5.8)	3.6 (3.1–4.1)	0.022

Results are given as median (range) or n/n.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; F, female; GGT, gamma-glutamyl transferase; HSC, hepatosplenic candidiasis; HSCT, hematopoietic stem cell transplant; M, male; TPN, total parenteral nutrition; TS, transferrin saturation.

5. Discussion

Infections are one of the major causes of morbidity and mortality in patients with hematological malignancies. IFI has become a significant problem in this group of patients with the emergence of more intensive cytotoxic regimens. HSC is a distinct form of IFI, which is extremely difficult to diagnose and manage. Blood cultures are positive in less than 50% of patients and biopsy may not be sufficient to demonstrate the fungal infection. Moreover, persistent neutropenia may mask the lesions and HSC might become invisible on imaging studies, such as CT scans.[2,3,8,12]

HSC was demonstrated in six (2.3%) patients in our study cohort. Although data concerning HSC in patients undergoing HSCT are limited, the incidence appears to have increased over time. The reported frequency of HSC ranges between 3% and 29%.[3,4,6,8] Autopsy findings have demonstrated a high HSC incidence in acute leukemia (3.8–6.8%) and in HSCT recipients (9%), as expected.[8]

HSC was more common in allogeneic HSCT recipients than autologous HSCT recipients and in patients who had received two or more chemotherapy courses prior to HSCT than in patients who had received fewer than two. Several predisposing factors have previously been described for HSC, including vascular devices, parenteral nutrition, mucositis, and intensive chemotherapy. Furthermore, younger age, prolonged neutropenia, and prophylactic use of quinolone antibiotics have been reported as independent risk factors for the development of HSC in patients with acute leukemia.[2,3] It has also been indicated that patients with GVHD have a tendency to acquire opportunistic infections, presumably due to the underlying T-cell defects or immunosuppressive treatment.[5,13] Poor PS has been considered to be an important prognostic factor for candidemia in cancer patients.[14] Similarly, the pre-HSCT PS of our patients with HSC was found to be worse than in patients without HSC.

Pre-transplantation serum ferritin levels were significantly higher in patients with HSC compared to patients without HSC, with increased levels of pre-HSCT acute phase reactants as well, indicating the presence of an inflammatory response. Ferritin, being an iron storage protein, has a critical role in iron homeostasis. It is currently the most used predictor of IO, as it is cost-effective and widely available. However, it is well known that ferritin may not be an accurate measure of total body iron burden in patients who have ongoing acute infectious or inflammatory conditions.[15–18]

Microorganisms require iron to survive, as iron is essential for microbial proliferation. It is postulated that excessive iron adversely affects the antimicrobial functions of neutrophils, monocytes, macrophages and natural killer cells, as well as immunoglobulin secretion and complement system function. It is therefore considered to be a risk factor for infections with various pathogens, including *Yersinia enterocolitica*, *Listeria monocytogenes*, Pseudomonas, Staphylococcus, Mucorales , *Vibrio vulnificus*, *Plasmodium falciparum*, *Mycobacterium tuberculosis*, *Mycobacterium avium* complex, *Candida albicans* and *Aspergillus* species.[1,9,10,13,15,19–26] Furthermore, based on the increased susceptibility to fungal infections in iron-overloaded states, iron chelation alone or combined with antifungal drugs are recommended for the prevention and treatment of fungal infections due to the antifungal effects of iron chelators.[27]

IO is a serious complication of HSCT and hematological malignancies.[16,23,28,29] Although iron is a critical element for cell growth, it may be potentially toxic to the host. In a state of iron excess, free iron acts as a free radical catalyzer, resulting in the formation of reactive oxygen species, which promotes the development of several complications. Iron increases the risk of infections, sinusoidal obstruction syndrome, hepatic dysfunction, mucositis, and idiopathic pneumonia syndrome in HSCT recipients.[10,16,20,30,31] IFIs in patients with IO have been reviewed extensively in 711 thalassemia patients who underwent HSCT, highlighting the role of transfusion burden and secondary hemochromatosis in infectious morbidity and mortality.[32] Iron-generated tissue damage is established to be partly mediated by non-transferrin bound iron (NTBI), indicating its more reliable predictive value in IO when compared to ferritin.[18,33–35] IO could be a significant contributor to treatment-related mortality in HSCT recipients.[10,16,28]

A history of previous IFI is a challenge for HSCT candidates, though not a contraindication.[36] Although prior HSC in patients with acute leukemia may not be an absolute contraindication for HSCT, a prophylactic antifungal approach is generally recommended.[2,8] The higher morbidity and mortality rates in patients with HSC and the enormous impact on the costs of HSCT, compell us to determine the subset of patients who are at high risk of developing HSC during the course of HSCT. It should be noted that serum ferritin is a sensitive but not a specific marker for IO and may be a poor predictor of excess tissue iron, particularly in the presence of infection and inflammation. The etiology of the elevated ferritin levels in our patients with HSC remains to be clarified. Although elevated ferritin levels appear to be a part of the acute phase reaction in our series, the inflammatory milieu of the patients may have masked a coexistent IO. The higher transferrin saturation ratio, though without statistical significance, suggests a possible role of IO. NTBI might be a more sensitive marker in predicting the role of IO in IFI. One other possibility is that the inflammatory response in the group of patients with HSC prior to transplantation might have been a sign of an occult systemic Candida infection, which presented with overt clinical signs with the recovery of neutrophils and immune functions after transplantation.

No matter the cause, high serum ferritin levels appear to define a subset of patients at increased risk of HSC. Whether the inflammatory state or IO, or a combination of these two, is the cause of hyperferritinemia remains to be elucidated. Pre-transplantation risk assessment and risk adapted strategies might lower the morbidity and mortality of IFI in HSCT recipients.

Conflict of interest

We have no competing interests to declare.

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