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Infliximab therapy in a patient with familial Mediterranean fever and chronic hip arthritis

To the Editor:

Familial Mediterranean fever (FMF) is an autosomal recessive disease in which arthritis attacks occur in about half of the patients, usually involving the ankle, knee, or hip (1,2). FMF arthritis is typically acute, episodic, and self-limited, resolving without sequelae; however, in ~10%, it is protracted, lasting 3 months to 7 years (3,4). Colchicine might not be effective when started after the development of arthritis, and, in such cases, therapeutic alternatives remain unclear and some patients require synovectomy (4). Arthritis in FMF can also be destructive, most commonly affecting hip joints, and might necessitate hip replacement (5,6). Here we report a patient with FMF and protracted hip arthritis who had an early response to infliximab therapy.

A 21-year-old woman with a history of FMF presented with severe right hip pain and difficulty walking. FMF was diagnosed at age 3 years when she began to have attacks of fever, abdominal pain, and arthritis, usually affecting the knees and ankles, and was started on colchicine therapy. At age 14 years, indomethacin was added for arthritis attacks lasting 4–5 days. Two years ago, colchicine and indomethacin were discontinued when she had an episode of bloody diarrhea that was self-limited. Biopsy of the duodenum was negative for amyloid. One week later, fever developed, followed by bilateral hip pain. An anteroposterior radiograph of the pelvis revealed significant joint space narrowing of the right hip (Figure 1). On magnetic resonance imaging (MRI) (Figure 2), coronal short inversion time inversion recovery images showed increased signal intensity consistent with bone marrow edema at the acetabulum bilaterally and at the lateral aspects of the left femoral head and neck. There was no evidence of joint effusion or synovial hypertrophy. Computerized tomography of the sacroiliac joints was normal. She was homozygote for M694V and was HLA–B27 negative. Colchicine 0.5 mg 3 times daily was restarted. Fever, abdominal pain, or diarrhea did not recur. However, right hip pain persisted, and 2 weeks later her followup erythrocyte sedimentation rate (ESR) was 110 mm/hour and the C-reactive protein (CRP) level was 96 mg/liter. Hip pain did not respond to nonsteroidal antiinflammatory drugs. Prednisolone 15 mg/day was started. A daily dose of 40 mg was required for pain control, which was accompanied by improvement in the ESR (13 mm/hour) and the CRP (6 mg/liter). Tapering off of steroid therapy was unsuccessful. She was allergic to sulfasalazine. Hydroxychloroquine and methotrexate (up to 20 mg weekly) were added, but the ESR and CRP level remained elevated, and the patient began to require assistance for ambulation.



Figure 1. Anteroposterior radiograph of the right hip demonstrated significant joint space narrowing without osteophytes and sclerosis.

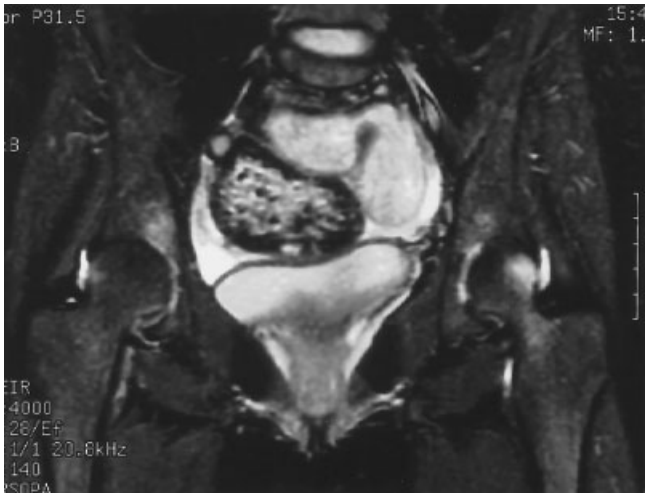


Figure 2. Coronal short inversion time inversion recovery magnetic resonance image of the hips demonstrated increased signal intensity consistent with bone marrow edema at the acetabulum bilaterally, and at the lateral aspects of the left femoral head and neck.

At the time of her current admission, she was afebrile. Her physical examination was unremarkable except for restricted and painful range of motion of the right hip joint. She weighed 50 kg. Her ESR was 60 mm/hour and the CRP level was 61 mg/liter. Results of the leukocyte

count, fasting blood glucose, and liver and kidney function tests were within normal ranges. On plain radiographs, there was progress in the joint space narrowing of the right hip. Repeat MRI demonstrated minimal effusion but no synovial hypertrophy, but did reveal irregularities of the cartilage of the right hip. There was minimal signal intensity change at the right acetabulum and the right femoral head, consistent with subchondral bone marrow edema. Due to the lack of efficacy of her current management, a tumor necrosis factor (TNF)–blocking agent, infliximab (200 mg) was given intravenously. She had a prompt response. In 4–5 days, she was able to ambulate independently. Two weeks later, her ESR was 20 mm/hour and the CRP value was negative (<6 mg/liter), and steroid therapy was discontinued. She initially received 3 doses of infliximab (at 0, 2, and 6 weeks); however, the effect was not sustained, and she required subsequent infusions approximately every 8–10 weeks. Thus far she has received 5 doses.

A patient with FMF and severe hip arthritis is described. The attack began while she was not receiving colchicine, and she did not respond to colchicine when it was given later. In this case, a coexistent juvenile idiopathic arthritis cannot be excluded. However, the nature of the arthritis, i.e., self-limiting attacks in joints other than the right hip, argues against it. Rapid loss of joint space width but absence of significant synovial hypertrophy, effusion, or erosions is also not typical of chronic arthritis. Conversely, prolonged duration of active disease (>2 years) is unusual for FMF. The patient did not experience any febrile abdominal attack during this period, but hip pain associated with elevated markers of inflammation was refractory. There are studies suggesting a role for TNFα in the pathogenesis of FMF (7,8), but the efficacy of TNF-blocking agents has not been previously reported. This patient did not respond to usual therapy for FMF, as well as medications used in other forms of chronic inflammatory arthritides, and she had a dramatic early response to infliximab, the only available TNF-blocking agent in this country at that time. The response appeared not to be sustained, lasting approximately 2 months.

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A new skip area in the diagnosis of temporal arteritis

To the Editor:

Temporal arteritis is a vasculitis of unknown etiology that occurs primarily in older individuals. Its clinical manifestations, physical findings, and laboratory abnormalities have been well defined. Arterial lesions tend to affect larger arteries of the head, neck, and upper torso in an irregular, segmental fashion. Hence the term "skip lesion" has been coined to describe the pathologic distribution of inflammation. The following case describes a new skip area in the diagnosis of temporal arteritis that has not been previously reported.

A 62-year-old woman reported a 4-week history of polymyalgia rheumatica, fatigue, a 7-pound weight loss, and a new mild frontal headache. Her laboratory data was remarkable for a hemoglobin of 10.8, an erythrocyte sedimentation rate of 85, and a platelet count of 506,000. Her physical examination showed a tender, left temporal artery that was pulsatile and without nodularity. Prednisone was started at 60 mg/day for a presumptive diagnosis of temporal arteritis, and a temporal artery biopsy was scheduled.

The surgeon performed the biopsy in his freestanding surgical center, and the specimen was sent to the local hospital pathology department for interpretation. Because the patient's insurance carrier (Blue Cross and Blue Shield of New Jersey) would not pay the hospital pathology department for specimen interpretation if the biopsy was performed at an outside facility, the specimen was "triaged" to the laboratory chosen by the insurance company, Laboratory Corporation of America (LabCorp). If the biopsy had been performed at the hospital, Blue Cross would have paid for the pathology interpretation in-house. LabCorp processed the temporal artery biopsy as "routine" and estimated a turnaround time of anywhere from 3–4 weeks, clearly an unacceptable time frame. Repeated calls to LabCorp were not able to change this protocol.

The biopsy report indicated no evidence of arteritis in a tangentially cut specimen. By this time, the patient had been taking prednisone for 4 weeks and was responding well. All of her symptoms had resolved, and her previous laboratory values had returned to normal. However, she was now diabetic with a fasting glucose of 191, and although clinically, temporal arteritis was still the diagnosis of choice, it had not been confirmed. The patient began to question the use of steroids without a definitive diagnosis.

Multiple attempts to find and communicate with the interpreting pathologist were futile. Blue Cross agreed to pay for a second opinion on the pathology so the original slides were sent back to the hospital. The specimen was reexamined and the internal elastic laminae, crucial for interpretation, were found to have been compromised. One small section was still intact and this was subsequently cut transversely. The pathology report confirmed the diagnosis of arteritis, and the patient was able to accept the need for steroids.

This case illustrates how insurance companies can disrupt the diagnostic process. By funneling work toward the "lowest bidder," valuable time is lost, mistakes are made, and in many cases, the diagnosing physician is removed from the loop. Rheumatologists must insist on excellence. We cannot allow "skip areas" along the way in pursuit of an accurate diagnosis. We need to be able to direct how and where temporal artery biopsies are handled and by whom. We should insist temporal artery biopsies be performed in the hospital where we feel most confident with the pathologist, where slides can be personally viewed, and where communication among all involved is easily accomplished. Accurate and timely pathology is an integral part of the diagnostic process and cannot be "skipped." Our patients deserve no less.

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Submissions Invited for Themed Issue of *Arthritis Care & Research:* Rheumatic Disease Through the Lifespan

Arthritis Care & Research is soliciting manuscripts for a themed issue addressing rheumatic disease through the lifespan. Manuscripts covering a broad range of topics related to the major theme are invited; for example, developmental and aging issues, risk factors at various ages, epidemiology of rheumatic disease across the lifespan, impact of disease on quality of life for specific age groups, and public health impact of rheumatic disease as a result of population aging. Submissions from a range of disciplines, from genetic epidemiology to public policy are welcome.

The issue will include regular submissions as well, but a certain number of pages will be reserved for articles accepted in response to this solicitation. All manuscripts will be peer-reviewed. All types of manuscripts (e.g., original articles, brief reports, case studies, trainee rounds, reviews) are included in this solicitation.

Manuscripts will be accepted for this issue beginning April 1, 2005. The deadline for submission is August 1, 2005. For further information, contact Edward Yelin, PhD (yelin2@itsa.ucsf.edu) or Patricia Katz, PhD (pkatz@itsa.ucsf.edu).