Pseudoseptic Arthritis with Low Synovial Fluid Glucose in Familial Mediterranean Fever

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Septic arthritis, a direct invasion by microorganisms to the joint, represents one of the relatively few rheumatologic medical emergencies, with damage to the articular cartilage occurring as early as 3 days into the course of the disease in cases of delayed diagnosis and/or treatment [1]. The clinical diagnosis of septic arthritis should always be confirmed by synovial fluid analysis, which will typically exhibit a turbid appearance, with high white blood cell (WBC) count, low glucose concentration and gram positive stain and culture. Practically, however, a decision to start empiric treatment for septic arthritis is frequently made on the basis of a high clinical suspicion in the presence of a significantly elevated synovial WBC count while cultures are pending. Low synovial fluid glucose, while not a prerequisite for the diagnosis, is widely held to be quite specific for septic arthritis, and yet, low levels of synovial fluid glucose have been reported in pseudoseptic arthritis related to crystal-induced arthritides, rheumatoid arthritis and other rheumatic conditions [2,3].

We present two patients with known familial Mediterranean fever (FMF), who presented with pseudoseptic arthritis and low synovial fluid glucose in the course of an FMF attack, which led to unnecessary surgical intervention in one case.

PATIENT DESCRIPTION

CASE 1

A 49 year old male was admitted to the orthopedic surgery department with monoarthritis of the right knee accompanied by fever and chills. He had been previously diagnosed with FMF along with his two siblings and was treated with 2 mg colchicine daily for over three decades. His disease had manifested as recurrent short attacks of knee or ankle monoarthritis once every 4-6 months, sometimes accompanied by erysipeloid erythema, which was treated by non-steroidal anti-inflammatory drugs (NSAIDs) or local glucocorticoid injection during attacks. Otherwise, his past medical history was unremarkable. His last arthritis attack started 2 days before the current admission and presented with fever of 38.7°C and sharp right knee pain and swelling unresponsive to NSAIDs. On admission, the patient's right knee was warm and extremely painful. It contained a large amount of effusion. Blood tests revealed WBC of 10,800/mm^3, C-reactive protein (CRP) of 193 mg/L (the normal range is < 6 mg/L) and glucose of 130 mg/dl. Synovial fluid analysis was remarkable for 107,000/mm^3 WBC with 97% neutrophils and a synovial glucose level of 0. No crystals were demonstrated on polarized light microscopy. Despite a negative gram stain, due to high clinical suspicion of septic arthritis, intravenous antibiotics were initiated. The next day, no clinical improvement was noted. With repeat aspiration, the synovial fluid WBC was 95,000/mm^3 and synovial glucose level was 37 mg/dl. The patient underwent arthroscopic surgery of the right knee and kept receiving wide spectrum antibiotics. Meanwhile, synovial fluid cultures and polymerase chain reaction (PCR) tests for bacterial and mycobacterial infections came back negative. Pseudoseptic arthritis related to FMF was suspected and oral prednisone at a dosage of 40 mg daily was added. There was immediate improvement in the patient's clinical state and steroids were tapered. Four weeks later the patient developed monoarthritis of the right ankle, accompanied with fever of 38.7°C and chills. Blood tests demonstrated leukocytosis of 15,000/mm^3, CRP levels of 90 mg/L, and a glucose reading of 111 mg/dl. Synovial fluid analysis showed 49,000/mm^3 WBCs, of which 97% were neutrophils and glucose levels of 40 mg/dl. Again, broad spectrum intravenous antibiotics were instituted, but with no improvement. Blood and synovial fluid cultures and PCR results were negative. The addition of systemic glucocorticoids again led to rapid and full resolution of the ankle arthritis. These episodes of pseudoseptic arthritis were believed to be a manifestation of uncontrolled FMF, and the patient was prescribed canakinumab. No episodes of arthritis have been seen for more than 1 year.

PATIENT DESCRIPTION

CASE 2

A 29 year old female patient with known FMF, homozygous for M694V, presented with swelling of her right knee, abdominal pain and fever of 39°C. Her past medi-

cal history was unremarkable, but she kept having rare attacks of FMF, mostly presenting as abdominal pain and fever, while being treated with 1.5 mg of colchicine daily. Two of her brothers and her father were also diagnosed with FMF. On physical examination, a large effusion of the right knee and diffuse tenderness of the abdomen were noted. Blood studies demonstrated normal WBC, CRP levels of 95 mg/L, and glucose readings of 80 mg/dl. Serum amyloid A levels were high, 530 mg/l (normal < 6.4 mg/l). Synovial fluid analysis revealed glucose levels of 30 mg/dl and WBC of 80,000/mm^3 with 95% neutrophils. Gram stain was negative. A course of broad spectrum intravenous antibiotics was initiated but later discontinued due to lack of efficacy and negative synovial fluid cultures, and PCR tests were negative for bacterial, mycobacterial and fungal agents. A dose of oral prednisone (0.5 mg/kg/day) was added and showed an immediate significant clinical and laboratory improvement.

COMMENT

Arthritis is a common feature of FMF attacks with the large joints of the lower extremity being most frequently involved. Classically, the arthritis of FMF is accompanied by other manifestations such as fever, abdominal pain and/or serositis. However, about 5% of FMF arthritis presents as mono- or oligoarthritis with no other FMF-related symptoms. This presentation is referred to as *protracted arthritis* [4]. The synovial fluid in FMF arthritis is sterile, ranging from cloudy to purulent, and contains a large percentage of neutrophils. Uthman and colleagues [5] have suggested that fever and monoarthritis in FMF may be confused with infection. To the best of our knowledge, low synovial glucose levels in FMF arthritis have not been previously reported. The mechanisms of diminished intra-articular glucose content in the course of acute but aseptic arthritis have not been elaborated, but in light of existing reports of low synovial glucose levels in pseudoseptic arthritis in patients in other rheumatic diseases, a common pathway of glucose consumption by the hyperinflamed synovium can be suggested.

The differentiation of pseudoseptic arthritis with very high WBC count in synovial fluid and low glucose levels from true septic arthritis has always been challenging, especially with biological medicines used widely for the treatment of rheumatic diseases. In this setting, joint infection caused by atypical or rarely seen agents, sometimes not easily grown in culture in the laboratory, should not be overlooked.

CONCLUSIONS

In summary, two patients with FMF pseudoseptic arthritis with low synovial fluid glucose are reported. Knowledge of this phenomenon can be useful in clinical practice and may prevent unnecessary invasive treatment for presumed joint infection in some patients.

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Capsule

Mediating effect of changes in hand impairments on hand function in patients with rheumatoid arthritis: exploring the mechanisms of an effective exercise program

To determine whether the effect of the Strengthening and Stretching for Rheumatoid Arthritis of the Hand (SARAH) exercise program on hand function was mediated by changes in the proposed active ingredients: strength, dexterity, and/or range of motion. The SARAH intervention included exercises hypothesized to improve potential mediators of grip strength, pinch strength, wrist flexion, wrist extension, finger flexion, finger extension, thumb opposition, and dexterity, which would theoretically improve self-reported hand function. All variables were measured at baseline and at 4 and 12 months. Structural equation modeling was used to assess mediation on change in hand function via change in potential mediators. Hall et al. found that change in grip strength partially mediated change in hand function. Grip strength mediated 19.4% (95% confidence interval 0.9%, 37.8%) of the treatment effect. Improvements in grip strength at 4 months are likely to mediate improved hand function at 12 months. The role of joint mobility exercises was less clear and was likely influenced by the choice of measurement tools for both mobility and function outcomes. More robust measurements of wrist and hand mobility for patients with rheumatoid arthritis may be necessary to determine the relationship between this variable and self-reported hand function. Using a large trial data set, we have demonstrated that techniques used to target grip strength are key active ingredients of the SARAH exercise program and mediate its effect.

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