CLINICAL VIGNETTE

Recurrent Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis in an Adult on Immunosuppressive Therapy

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A 20-year-old male with an 8-year history of autoimmune hepatitis in remission maintained on 6-mercaptopurine presented with recurrent episodes of high fever up to 39.4C and painful cervical lymphadenopathy. During his childhood, the patient had similar episodes of fever and cervical lymphadenopathy on a near monthly basis. These episodes essentially resolved spontaneously after the age of 8. At age 12, the patient was diagnosed with autoimmune hepatitis. He was successfully managed on 6-mercaptopurine 50mg per day. At age 18, he underwent a liver biopsy, which showed that his autoimmune hepatitis to be in remission. At age 19, the patient began having recurrent episodes of high fevers, pharyngitis with lymphadenopathy. On examination, he has bilateral enlarged tonsils with whitish exudates and tender cervical lymph nodes. Repeated bacterial, viral, and fungal throat cultures were negative. He had 5 episodes within a span of 6 months. He was treated with multiple courses of antibiotics with minimal improvement. Immunological evaluation was negative. The patient was suspected to have periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) without stomatitis, and he was treated with a single dose of prednisone 60mg. The diagnosis was confirmed after rapid resolution of his symptoms after the single dose of steroids. His dose of 6-mercaptopurine was eventually reduced to 25mg per day with significant reduction in frequency of the febrile episodes. Over the past several years, the patient has had at the most 1-2 episodes per year.

PFAPA is a chronic disease characterized by periodic episodes of high fever, aphthous stomatitis, pharyngitis, and cervical adenitits. First recognized in children, the condition was defined by Marshall in 1987.[1] The diagnostic criteria of PFAPA syndrome was modified by Thomas et al in 1999 and by Padeh S in 2005 (Table 1).[2,3] The condition is characterized by high fevers of sudden onset accompanied by pharyngitis and cervical adenititis. Aphthous stomatitis of the buccal mucosa occurs less frequently in only 38-75% of the patients.[4] Prodromal symptoms may precede the main symptoms of malaise, irritability, and fatigue.[5] Other symptoms include headache, diarrhea, arthralgia, rash, chills, and abdominal pain.

An adult case of the condition was first reported by Cavuto and Bonagura in 2008 and later in a series by Padeh as well as Cantarini.[6,7,8] The mean age of onset was 20.9 years and attacks tend to recur every 4-6 weeks with a complete resolution of symptoms in between the episodes.[6] When compared to children, adults typically have lower rates of aphthosis and chills but higher rate of arthralgias and myalgias.[6]

The cause of the condition remains unknown. No genetic abnormalities have been described, but there have been some positive family history reported in studies involving siblings.[9,10] There is no specific laboratory testing for PFAPA. The patients may have elevated white blood cell counts. At onset of the fever, inflammatory markers such ESR may initially be normal but become elevated over a few days.[5] In addition to negative throat cultures, urine and blood cultures are also normal. Based on the current criteria, the diagnosis of PFAPA remains clinical. In addition to ruling out infectious causes, differential diagnoses include cyclic neutropenia, familial Mediterranean fever, and hyperimmunoglobulin D syndrome, Tumor Necrosis Factor receptor associated periodic syndrome (TRAPS), cryopyrin associated periodic fever syndrome (CAPS), and immunodeficiency syndromes.

The mainstay of treatment is a single, high-dose of corticosteroid, typically 60mg of prednisone. All patients report a dramatic resolution of fever within 2-4 hours after one dose of corticosteroids at the onset of each episode. This feature is unique to this syndrome. Tonsillectomy had previously been associated with resolution of PFAPA recurrences. However, more recent studies with longer follow-up found that the failure rate can be as high as 33%, so tonsillectomy is no longer recommended.[5,7] Prophylactic therapies with colchicine showed some promise in extending the interval between the attacks but did not induce a complete remission.[11] Cimetidine has also been investigated and found to have limited efficacy.[5]

PFAPA should be considered in any adult with unexplained recurrent episodes of fever and other corresponding symptoms. This case highlights several interesting points. As with other reports, the patient has met all the diagnostic criteria except for aphthosis, which has been identified to occur less frequently in adults. In addition, this is an example of childhood PFAPA, which had essentially gone into remission after age 8 but recurred during adulthood over a

decade later. Since the reduction in the dosage of 6-mercaptopurine is associated with a significant decrease in the frequency of attacks, the recurrence is possibly related to the use of concomitant immunosuppressive therapy.

Tables

Table 1. Diagnostic criteria of PFAPA syndrome.

Monthly fevers – cyclic fever at any age group
Exudative tonsillitis with negative throat cultures
Cervical lymphadenitis
Possible aphthous stomatitis
Completely asymptomatic interval between episodes
Rapid response to a single dose of corticosteroids (60mg prednisone)

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