CLINICAL VIGNETTE

A Pediatric Disease in an Adult Patient

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Case Report

A 19-year-old female presented to the rheumatology for an autoimmune evaluation. In the past few months, she had developed recurrent low-grade fevers, sore throat and cervical lymphadenopathy. She was first seen in urgent care and given a course of amoxicillin for presumed infection. The episodes of fever, sore throat and lymphadenopathy persisted and worsened to include myalgias, chills, night sweats and severe fatigue. She saw an Ear Nose and Throat specialist who ordered additional studies, including negative throat culture and negative for COVID, mono, flu, cocci, bartonella, hepatitis and HIV serologies. ASO and DNase antibodies were also negative. Inflammatory markers were elevated and ANA was positive at a titer of 1:160 speckled, prompting rheumatology referral to evaluate for underlying autoimmune disease.

The patient had no significant past medical or surgical history. Prior to her illness she was in good health playing soccer for her university team. Her only medications were OTC ibuprofen and acetaminophen which she had been taking regularly to help manage the recurrent fevers and myalgias. She did not smoke, drink alcohol or use illicit drugs. Her family history was only significant for a father with multiple sclerosis. On review of systems, she had no history of alopecia, oral ulcers, sicca symptoms, pleurisy, raynauds or joint swelling. On exam, there was mild submandibular gland swelling but was otherwise normal. Additional autoimmune serologies included negative ANCA, RF, CCP, dsDNA, Sm/RNP, SSA/B, centromere, Scl-70, Mi-2, Jo-1 neg, cardiolipin, TPO, thyroglobulin, histone and celiac antibodies. ACE levels were normal. Serum protein electrophoresis and immunofixation were also normal.

Her symptoms progressed, and she was hospitalized for high grade fevers and severe nausea and vomiting. She was given supportive care with parenteral fluids, ondansetron and analgesics. Infectious disease, Oncology and Rheumatology consulted to evaluate fever of unknown origin. White count was slightly elevated at 10.2 but CBC was normal as well as metabolic panel. Sedimentation rate and CRP were elevated at 84/hr and 19.3. Blood Cultures, anaerobic cultures, fungal cultures, MRSA, stool cultures, stool O&P and urine cultures were all normal. CT of the chest, abdomen and pelvis showed hepatosplenomegaly but was otherwise normal. CT of the neck showed enlarged tonsils and cervical lymphadenopathy consistent with inflammatory lymphadenitis with mass effect on the bilateral internal jugular veins. Excisional biopsy of a cervical lymph node demonstrates necrotizing granulomatous inflammation. AFB and GMS stains were normal and there was no pathologic evidence of malignancy.

She was discharged from the hospital and prescribed prednisone which has helped control her symptoms. Genetic testing was submitted to rule out autoinflammatory fever syndromes and resulted as normal. After review of the entire clinical picture, she was diagnosed with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) syndrome. Cimetidine was prescribed with subsequent reduction of flare severity and frequency.

Discussion

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) is a chronic disease of unknown etiology. It is thought to be caused by inadequate activation of the innate immune system with no associated infectious or autoimmune triggers.[1] It belongs to a group of periodic fever syndromes that has been well described in pediatric patients and include familial mediterranean fever (FMF), HyperIgD syndrome and tumor necrosis factor receptor-associated periodic syndrome (TRAPS) among others. However, it is a non-hereditary syndrome differs from these autoinflammatory fevers.[2]

Clinical evaluation remains the mainstay of diagnosis of PFAPA.[3] PFAPA is characterized by periodic episodes of fever, usually with an abrupt onset, accompanied by at least one of the following cardinal manifestations: pharyngitis, aphthous stomatitis and cervical adenitis as described by the PFAPA acronym. In children these episodes last on average 4 days and return with a clockwork periodicity every 2-8 weeks. Both children and adults are asymptomatic between episodes. During crises, patients usually show moderate leukocytosis and elevated inflammatory markers[1] with typically normal laboratory results in between flares. A dramatic response to a single oral dose of corticosteroids is also unique to this syndrome[2] and can be helpful in distinguishing PFAPA from other etiologies.

In PFAPA, 90% of cases occur before the age of 5.[3] PFAPA remits spontaneously in most patients by the age of 10 but a small subset of patients continue to be symptomatic into adolescence. While adult onset of PFAPA is rare,[1] cases in adults are being increasingly recognized and diagnosed.[3] There are a few clinical differences that have been reported between childhood and adult onset PFAPA. The frequency of flares is significantly

higher in pediatric cases, while febrile attack duration is longer in adults. Clockwork periodicity of fever and recurrent pharyngitis is also more frequently observed in children. Other systemic symptoms such joint pains, myalgia, fatigue, headache, ocular signs and rashes were more common in adults.[4] In addition, the complete resolution of flares after a single steroid administration was less pronounced in adults than among pediatric patients.[5]

PFAPA syndrome is recognized more frequently in children and therefore diagnostic delay is strikingly higher in adults.[3] Even though rare, it is crucial to differentiate PFAPA from other causes of periodic fever in adults in order to avoid extensive diagnostic testing and unnecessary antibiotic therapy.[1] Among patients presenting with recurrent fever of unknown origin, the presence of erythematous pharyngitis and/or cervical lymphadenitis with elevated inflammatory markers and symptom-free intervals are the variables most strongly correlated with PFAPA. However, these clinical principles should be applied after having ruled out known causes of fever including infective, autoimmune and neoplastic diseases as well as other auto-inflammatory conditions.[5]

PFAPA syndrome is usually a benign and self-limited disease which resolves without long-term sequelae.[1] Optimal treatment is not yet established.[3] Usually glucocorticoids are the main choice for episodic therapy, since most patients experience rapid resolution of symptoms after a single dose of prednisone 1mg/kg or equivalent when taken at the onset of the fever.[1] Steroids, though, do not prevent future PFAPA episodes from recuring.[3] Some patients may benefit from prophylactic therapy with colchicine or cimetidine.[1] There have also been reports that tonsillectomy may induce remission or decrease symptoms in PFAPA, although this was found to be less useful in adults than in children.[3]

In conclusion, PFAPA syndrome should be considered in patients presenting with recurrent unexplained episodes of fever after more serious and common conditions, particularly recurrent infections and malignancies, have been excluded, regardless of the patient's age.[3]

REFERENCES

1. **Marques DP, Rocha S, Manso M, Domingos R**. Periodic Fever with Pharyngitis, Aphthous Stomatitis and Cervical Adenitis Syndrome: A Rare Cause of Fever in Adults. *Eur J Case Rep Intern Med*. 2019 Mar 8;6(3):001041. doi: 10.12890/2019_001041. PMID: 30931275; PMCID: PMC6438113.
2. **Padeh S, Stoffman N, Berkun Y**. Periodic fever accompanied by aphthous stomatitis, pharyngitis and cervical adenitis syndrome (PFAPA syndrome) in adults. *Isr Med Assoc J*. 2008 May;10(5):358-60. PMID: 18605359.
3. **Ferreira Cristina S, Costa A, Toscano M, Kakoo Brioso E, Cipriano P.** Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis Syndrome: A Rare Etiology of Fever in Adults. *Cureus*. 2021 Apr 29;13(4):e14749. doi: 10.7759/cureus.14749. PMID: 34084676; PMCID: PMC8164374.
4. **Rigante D, Vitale A, Natale MF, Lopalco G, Andreozzi L, Frediani B, D'Errico F, Iannone F, Cantarini L**. A comprehensive comparison between pediatric and adult patients with periodic fever, aphthous stomatitis, pharyngitis, and cervical adenopathy (PFAPA) syndrome. *Clin Rheumatol*. 2017 Feb;36(2):463-468. doi: 10.1007/s10067-016-3317-7. Epub 2016 Jun 1. PMID: 27251674.
5. **Cantarini L, Vitale A, Sicignano LL, Emmi G, Verrecchia E, Patisso I, Cerrito L, Fabiani C, Cevenini G, Frediani B, Galeazzi M, Rigante D, Manna R**. Diagnostic Criteria for Adult-Onset Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Cervical Adenitis (PFAPA) Syndrome. *Front Immunol*. 2017 Aug 24;8:1018. doi: 10.3389/fimmu.2017.01018. PMID: 28970828; PMCID: PMC5609591.