

Case Report

Cyclical Fevers in a 4-year-old Boy with IgA Deficiency

Joshua Y.C. Yang 

Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA; joshua@jhu.edu; Tel.: +1-619-944-9009

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Abstract: While immunodeficiencies, such as (Immunoglobulin A) IgA deficiency, may predispose pediatric patients to respiratory illnesses, they are also associated with autoinflammatory conditions. Distinguishing between these possible complications requires an awareness of these uncommon conditions. We report a case of a four-year-old boy with a history of IgA deficiency presenting to his primary care provider with fever of one week's duration accompanied by abdominal, ear, and throat pain. The patient's mother reported that he had these symptoms twice a month for the prior ten months during which he occasionally developed oral ulcers. Between episodes, the patient fully recovered without complications. Considering the patient's history of IgA deficiency, it was originally assumed that the patient had strep throat and coincidental resolution of his symptoms after initiation of antibiotic therapy supported this diagnosis. However, due to the recurrent nature of his symptoms, a preliminary diagnosis of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) was made. A referral to an otolaryngologist was made, and findings of adenopathy and tonsillitis suggestive of PFAPA were confirmed. The patient was scheduled for adenoidectomy and tonsillectomy, which were performed without complication, leading to the cessation of these episodes.

Keywords: PFAPA; periodic fever; aphthous stomatitis; pharyngitis; adenitis; pediatric; recurrent fever syndromes; IgA deficiency

1. Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) is a rare childhood disease, although the most common of the recurrent fever syndromes, that presents with repeated episodes of fever as well as oral sores, swollen lymph nodes, and sore throat [1]. Although the etiology is not known and there is no standard laboratory test to confirm diagnosis [2], it has been established that PFAPA has a non-monogenic mode of inheritance and familial susceptibility [3]. While PFAPA is classified as an autoinflammatory disease, marked by the key role that the cytokine IL-1 plays in the disease [4], there are instances in which an immune deficiency may be considered a risk factor for the disease [5]. Herein, we report on the first case in the medical literature of a case of PFAPA in the context of IgA deficiency, an immunodeficiency characterized by the development of eczematous and autoimmune diseases [6,7].

2. Case Presentation

2.1. Clinical Presentation

A four-year-old Caucasian boy with a history of eczema, seasonal and dust mite allergies and a neonatally-diagnosed selective IgA deficiency presented to his primary care provider with fever of one week's duration accompanied by abdominal, ear, and throat pain. Three weeks prior to this visit, he presented to the clinic with a similar set of symptoms that appeared to resolve after his pediatrician started him on amoxicillin and clavulanic acid for presumed streptococcal pharyngitis. The

patient's mother reported that he had these symptoms twice a month for the past ten months during which he occasionally developed oral ulcers. Between these episodes, the patient fully recovered without complications.

Physical examination revealed a temperature of 101.5 °F, other vital signs were within normal limits. On examination, there was lymphadenopathy bilaterally, visibly enlarged tonsils, and clear nasal discharge. Cardiovascular examination was unremarkable: normal palpation of the heart, PMI was nondisplaced, and auscultation of the heart found regular rate without murmurs, rubs, or gallops. Neurologic exam was also normal, with a grossly non-focal neurologic exam. The patient's mental status was alert, age-appropriate, and with normal mood and affect. Motor strength was normal, and the patient denied any numbness or weakness of arms or legs. The remainder of the examination findings were normal.

2.2. Laboratory Investigations

Standard laboratory panels were performed by LabCorp and included a complete blood count with differential/platelet, comprehensive metabolic panel, immunoglobulin A/G/M quantification, Lyme disease antibody/Western, C-reactive protein quantification, and total complement quantification. Initial laboratory evaluation showed normal electrolyte levels with a C-reactive protein level of <0.3 mg/L and a total complement level of 57 U/mL. The complete blood count showed lymphocytosis (6400/ μ L) and eosinophilia (400/ μ L). Serum IgG and IgM were within the normal range (656 and 47 mg/dL, respectively), serum IgE was elevated (71 IU/mL), and serum IgA was low (9 mg/dL). Both a rapid strep test and the Lyme disease test results were negative.

Because of these recurrent symptoms, he was referred to an otolaryngologist, who performed a surgical procedure that resulted in resolution of his upper respiratory tract symptoms. The patient was diagnosed based on the clinical findings and the exclusion of other diseases.

2.3. Differential Diagnosis and Clinical Course

Considering the patient's history of congenital IgA deficiency, it was originally assumed that the patient had strep throat and coincidental resolution of his symptoms after initiation of antibiotic therapy supported this diagnosis.

However, due to the recurrent nature of his symptoms, other diagnoses were considered. The differential diagnosis for a pediatric patient presenting with distinctive pharyngitis and lymphadenopathy centers largely around viral and bacterial causes, including viral pharyngitis, streptococcal pharyngitis (strep throat), and possible zoonotic causes, such as tularemia and cat-scratch disease (bartonellosis). We also considered and tested for Lyme disease because its presentation may include periodic fever [8]. Exclusion of Lyme disease was necessary for the differential diagnosis process because the treatment options available would have been contraindicated in some diagnoses. For example, corticosteroids are a treatment option in recurrent fever syndromes but has been reported to increase Lyme disease severity [9,10].

Although the patient did not have any active aphthous ulcers at this most proximal visit, the patient's history of recurrent ulcers suggested several potential autoimmune and autoinflammatory diseases. In the pediatric population, such diseases include inflammatory bowel disease (IBD) [11], Behçet disease [12], recurrent fever syndromes, such as cyclic neutropenia [13] and PFAPA [14], and systemic lupus erythematosus (SLE) [15]. The lack of arthritis or chronic anemia did not support a diagnosis of IBD while the absence of genital ulcers, ophthalmic lesions, and skin lesions opposed a diagnosis of Behçet disease. A lack of diagnostic hallmarks for SLE, inclusive of malar rash, arthritis, and hematologic deficiencies (i.e., hemolytic anemia, thrombocytopenia, leukopenia, or lymphopenia) was not supportive of a diagnosis of SLE. While recurrent fever, pharyngitis, and oral ulcers could support either cyclic neutropenia or PFAPA, absolute neutrophil counts on multiple days were all in the normal range. Furthermore, a lack of recurrent skin infections, occurring in more than 80% of people with cyclic neutropenia [16], did not support this diagnosis.

After the exclusion of these and other common and uncommon potential diagnoses, a preliminary diagnosis of periodic fever, with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) was made. A referral to an otolaryngologist was made, and findings of adenopathy and tonsillitis suggestive of PFAPA were confirmed. Our patient was scheduled for adenoidectomy and tonsillectomy which were performed without complication.

His upper respiratory tract symptoms resolved after surgery and no cyclical recurrences have been reported at his postoperative and well-child care visits.

3. Discussion

PFAPA is the most common member of a set of autoinflammatory diseases known as recurrent fever syndromes. While most of these have a known monogenic cause [17], the etiology of PFAPA is unknown and suspected to be multifactorial [18]. This is a chronic disease typically occurring in young children under the age of five years old and is characterized by high fevers at four to six-week intervals accompanied by aphthous ulcers, pharyngitis, and cervical adenitis. In between episodes, patients are typically healthy [14].

Besides the hallmark of fever, pharyngitis is the most common associated symptom and can be erythematous or exudative. Cultures and rapid antigen tests are negative. The aphthous ulcers, occurring in 40–70% of patients and usually on the lips or buccal mucosa, typically precede the development of and disappear with the initiation of fever. Other non-specific symptoms include headache, abdominal pain, nausea, vomiting and myalgias [1].

While the diagnosis of PFAPA is clinical in nature, laboratory findings may be helpful in narrowing the diagnosis. Leukocytosis, elevated ESR, and elevated C-reactive protein can be seen during episodes but return to baseline between recurrences [14]. Notably, serial CBCs should not reflect cyclic decreases in neutrophil levels, as this would serve to diagnose cyclic neutropenia, a rare immunodeficiency that presents with similar symptoms [19]. Imaging modalities, such as CXR and CT, are not useful in diagnosis.

While PFAPA is typically associated with increased immunoglobulin levels, typically IgD and IgE but also IgM and IgA [1], our patient has IgA deficiency, a condition that predisposes individuals to both atopic and autoinflammatory diseases. Among individuals with IgA deficiency, 10–15% will develop an allergic disease and 25–33% will develop an autoimmune disease [1]. This is a presentation consistent with our patient's past medical history of eczema and allergies, laboratory findings of eosinophilia and elevated IgE, and current diagnosis of PFAPA.

Ultimately, the diagnosis of PFAPA remains dependent on clinical suspicion and findings involving the presence of at least three documented episodes of recurrent fevers with aphthous stomatitis, pharyngitis, and/or cervical lymphadenopathy with the exclusion of upper respiratory tract infection, cyclic neutropenia, and other identifiable hereditary autoinflammatory diseases.

Most cases of PFAPA are self-limited and will resolve by adolescence with no long-term sequelae. Due to the relative rarity of this condition, guidelines for medical treatment are largely empirical. Episodes of PFAPA can be treated with oral glucocorticoids, such as prednisone which rapidly relieves the fever and pharyngitis [1]. However, glucocorticoid treatment has been noted to reduce the intervals between episodes and lead to more total episodes. Preventive treatment with either cimetidine or colchicine has been noted in small studies and case reports to reduce the intervals between fever episodes [20,21]. Recent reports have found anakinra, an IL-1 receptor antagonist also leads to clinical improvement [4]. A lack of responsiveness to antibiotics, NSAIDs, and antivirals suggests the importance of recognizing PFAPA to prevent prescription of unnecessary therapeutics.

For disease refractory to conservative medical treatments, tonsillectomy with or without adenoidectomy has been shown in small randomized trials to result in immediate and complete resolution of symptoms with a number needed to the benefit of 1.89 (the number of patients that need to be treated for one of them to benefit compared with a control). Further, the mean length of episodes decreased from 3.5 days to 1.7 days after tonsillectomy [22,23]. However, the possible benefits

of tonsillectomy must be balanced with the inherent risks of the procedure as the disease typically self-remits by ten years of age [23,24].

4. Conclusions

A diagnosis of PFAPA should be considered in a patient presenting with recurrent fevers, aphthous ulcers, pharyngitis, and adenopathy. Other concurrent illnesses that are risk factors for autoimmune or autoinflammatory disease, such as IgA deficiency, can serve as a clue to the diagnosis. Diagnosis is made clinically with the presence of aphthous stomatitis, pharyngitis and cervical lymphadenopathy and exclusion of upper respiratory tract infection, cyclic neutropenia, or other hereditary periodic fever syndromes. Medical management with prednisone or cimetidine is appropriate first-line therapy. In severe or refractory cases, adenoidectomy and tonsillectomy have been shown to result in resolution of symptoms.

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