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Adult-Onset PFAPA Syndrome: Successful Management with Colchicine

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 22-year-old
Final Diagnosis: Periodic fever • aphthous stomatitis • pharyngitis • cervical adenitis (PFAPA) syndrome
Symptoms: Recurrent fevers associated with sore throat, enlarged painful cervical lymph nodes
Clinical Procedure: —
Specialty: Rheumatology

Objective: Unusual clinical course

Background: Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is an autoinflammatory fever syndrome primarily seen in children under age 5 years, and its etiology is unknown. Most cases are resolved by the age of 10 years, and it is rare in adults. PFAPA is characterized by recurrent episodes of fever associated with pharyngitis, stomatitis, and cervical adenitis, although not all clinical features are present at initial evaluation. Diagnosis is made clinically, as there are no specific biomarkers available. Treatment includes prednisone, colchicine, interleukin-1 blockers, and tonsillectomy. We report a case of adult-onset PFAPA syndrome that responded to colchicine.

Case Report: A 22-year-old woman presented to the Rheumatology Clinic for evaluation of recurrent fevers associated with sore throat and enlarged painful cervical lymph nodes. She was symptom-free between the episodes. Workup for infectious causes and autoinflammatory/autoimmune diseases was unremarkable. Various differential diagnoses were considered, due to her unusual presentation. After all were ruled out, PFAPA was diagnosed based on her symptoms, and she started steroids, to which she had a dramatic response and resolution of symptoms. She was then transitioned to oral colchicine, which significantly decreased flare frequency.

Conclusions: Being aware of PFAPA syndrome in adults is vital. A timely diagnosis can significantly improve a patient's quality of life. This case highlights the importance of considering PFAPA syndrome in the differential diagnosis of periodic febrile illnesses in adults and the role of Colchicine as prophylaxis. Larger studies are needed to understand etiopathogenesis better and develop other effective therapeutics.

Keywords: Steroids • Colchicine • Interleukin-1beta (204-215) • Periodic Fever, Familial, Autosomal Dominant

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/943658

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Introduction

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is an autoinflammatory fever syndrome mostly seen in children under 5 years of age and is rare in adults. It was initially called Marshall's syndrome until the acronym PFAPA was proposed in 1989 [1]. The etiology of the disease is still unknown, and the diagnosis is made clinically [2]. There are some differences between adult and pediatric PFAPA patients. Treatment includes corticosteroids and tonsillectomy. We report a case of adult-onset PFAPA syndrome that responded to colchicine.

Case Report

A 22-year-old woman presented to the Rheumatology Clinic for evaluation of recurrent fevers associated with sore throat and enlarged painful cervical lymph nodes. These episodes recurred every 4 weeks and lasted for 3 to 7 days. Symptoms were accompanied by headache and occasionally enlarged inguinal lymph nodes. There was no history of aphthous stomatitis. She was symptom-free between the episodes, and her lymph nodes regressed to normal size. She had no family history of periodic fever syndromes and no Mediterranean ancestry. The physical examination was unremarkable at the time of initial evaluation. The complete blood count was unremarkable, including the absolute neutrophil count and normal inflammatory markers. Infectious workup was negative, including HIV, chronic hepatitis B and C, tuberculosis Quantiferon gold, gonorrhea/chlamydia, Bartonella, and Epstein-Barr Virus serologies. She had an inguinal lymph node biopsy, which was negative for any malignancies. The autoinflammatory genetic profile was negative. Autoimmune disease workup was also unremarkable, including negative antinuclear antibodies, antineutrophilic cytoplasmic antibodies, and rheumatoid arthritis serologies. She had a dramatic response to just 1 dose of prednisone 60 mg daily, with complete resolution of her symptoms during a flare. PFAPA syndrome was diagnosed based on her history and significant response to prednisone. She continued to have recurrent episodes, so she was started on colchicine 0.6 mg twice daily, which led to a significant decrease in the frequency of these inflammatory episodes, and she had just 1 flare in the first 6 months after starting colchicine.

Discussion

PFAPA syndrome is a periodic fever syndrome, and its prevalence is rare in adults, explaining the delay in diagnosis [3]. The etiopathogenesis is unknown, but it has polygenic inheritance as opposed to monogenic inheritance of familial Mediterranean fever [4,5]. It has a slight male preponderance [1]. Periodic fever is the hallmark feature, and episodes usually last 3 to 7 days and recur every 2 to 8 weeks [6]. Aphthous ulcers usually occur on the buccal mucosa or the lips in approximately 40% to 70% of patients [3]. Pharyngitis with tonsillar exudates and cervical adenopathy usually occur with fever episodes [7]. The clinical phenotype seems similar in the adult and pediatric populations, with some prominent differences [1]. Adults tend to have more arthralgia and myalgia during flares [1]. The frequency of flares is higher in children, whereas the fever duration is higher in adults [8]. The occurrence of only 1 cardinal manifestation is more frequent in adults [3]. The diagnosis is mostly clinical, as there are no specific biomarkers. Modified Marshall's criteria (**Table 1**) proposed in 1999 have good sensitivity but lack specificity [1,9]. Our patient met these clinical criteria, and infectious causes were ruled out.

Table 1. Modified Marshall's criteria.

Criteria set	Modified Marshall's criteria
Age at onset	<5 years
Definition of "recurrent fever"	• Regularly recurring fevers
Symptoms	≥1/3 • Aphthous stomatitis • Cervical lymphadenitis • Pharyngitis
Inter-attack periods	• Completely asymptomatic • Normal growth and development
Exclusions	• Cyclic neutropenia • Upper respiratory tract infection

Differential diagnosis of PFAPA syndrome is broad, including infections, malignancies, systemic autoimmune diseases, and other autoinflammatory syndromes, such as familial Mediterranean fever. In our case, extensive infectious workup was negative, and the autoantibody profile was unremarkable. The patient did not have erysipelas-like rash or symptoms of serositis, which are cardinal features of familial Mediterranean fever, and FMF gene mutation was negative in the autoinflammatory panel.

Pediatric PFAPA syndrome is a self-limited disease with no long-term sequelae, although studies in adults are lacking [10-12]. Glucocorticoids are the first-line treatment, with symptoms improving within 24 h after a single dose of prednisone (1-2 mg/kg) [13] but cannot prevent subsequent fever flares [13]. There are multiple small studies on the use of colchicine in the pediatric population [10,14-16], but only limited evidence in the adult population [17-19]. It is postulated that there is upregulation of IL-1 beta in PFAPA syndrome, and colchicine acts through its inhibitory effect on the nucleotide-binding

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domain, leucine-rich repeat/pyrin domain-containing-3 inflammasome and IL-1 beta production [20]. Colchicine worked effectively in our case, with a substantial decrease in the number of flares, and we used 0.6 mg twice daily dosing as opposed to the dose used in other case reports [18]. IL-1 blockade with anakinra and canakinumab has been a recent development in PFAPA treatment, due to the association of elevated IL-1 beta-related transcripts during PFAPA flares [21-24]. Many studies support tonsillectomy with or without adenoidectomy in controlling symptoms or inducing remission, but attacks can recur after the surgery. Tonsillectomy seems less effective in adults than in children [25].

Conclusions

Adult-onset PFAPA syndrome is rare, and physicians are even less aware of it. It is a clinical diagnosis, but the lack of a 1 specific clinical feature should not preclude making the diagnosis if the clinical picture is otherwise highly suggestive of it. Colchicine has a potential prophylactic role, but larger studies are required for a definitive therapeutic assessment.

Department and Institution Where Work Was Performed

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