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Periodic Fever with Pharyngitis, Aphthous Stomatitis and Cervical Adenitis Syndrome: A Rare Cause of Fever in Adults

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ABSTRACT

Periodic fever with pharyngitis, aphthous stomatitis and cervical adenitis (PFAPA syndrome) is a common cause of periodic fever in children and usually manifests as episodes of fever recurring with a clockwork periodicity. Although rare after adolescence, adult patients with PFAPA syndrome may present with a wider range of symptoms and may lack the clockwork periodicity of fever. A 24-year-old patient presented with a 4-year history of periodic fever with pharyngitis and cervical adenitis. She also complained of vomiting, fatigue and sporadically presented with aphthous stomatitis. During crises, laboratory evaluation showed a moderate elevation of inflammatory markers. Blood cultures and ANA titres were negative. Immunoglobulins and serum ferritin levels were normal. After other causes of periodic fever had been excluded, a diagnosis of PFAPA syndrome was made.

LEARNING POINTS

- PFAPA syndrome is characterized by periodic fever accompanied by pharyngitis, aphthous stomatitis and cervical adenitis.
- It is a common cause of periodic fever in children but can also present in adults with a wider range of clinical manifestations.
- Establishing a firm diagnosis of PFAPA syndrome may avoid excessive work-up and potentially harmful treatment.

KEYWORDS

Periodic fever with pharyngitis, aphthous stomatitis and cervical adenitis, PFAPA syndrome, adults

INTRODUCTION

PFAPA syndrome is a common cause of periodic fever in children[1]. While it remits spontaneously in most patients before the age of 10, a small subset of patients may continue to be symptomatic into adolescence[2]. Rarely, patients have onset of periodic fever in adulthood[2]. Adults with PFAPA syndrome have a wider range of clinical manifestations[3].
We present a case of PFAPA syndrome in a young adult with a 4-year history of periodic fever and multiple cycles of antibiotic therapy.

CASE DESCRIPTON

A 24-year old woman presented to an outpatient setting with a 4-year history of periodic fever. The attacks were characterized by an abrupt onset of fever (maximum temperature of 40ºC), fatigue, malaise, myalgia, odynophagia, nausea and vomiting. Two of these crises had also been accompanied by oral aphthous ulcers. No other symptoms were reported. These symptoms lasted for 4 days and recurred every 3–4 weeks, although crises did not show clockwork periodicity. The patient had normal psychomotor development and was asymptomatic between crises.

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Physical examination performed during the symptomatic phase showed non-exudative pharyngitis and a right submandibular lymph node 1–2 cm in diameter. There were no other relevant physical findings. Laboratory evaluation showed mildly elevated inflammatory markers (mean leucocyte count 15,850/µl, mean neutrophil count 12,690/µl, mean C-reactive protein level 13.3 mg/dl) with normal procalcitonin levels (<0.05 ng/ml). There was no evidence of neutropenia immediately before or during crises. Chest x-ray showed no opacities or pleural effusion. Physical examination and laboratorial evaluation were normal between crises.

Subsequent investigation showed normal complement and serum ferritin levels, negative ANA titres and normal IgG, IgA, IgM and IgD levels. HIV serology and blood cultures were negative and there was no evidence of an infectious cause of prolonged fever (*Borrelia burgdorferi*, *Coxiella burnetii*, *Bartonella* spp., *Rickettsia* spp. and *Treponema pallidum* serology were negative; *Cytomegalovirus* and Epstein-Barr virus serology showed past infection). No throat cultures were performed. The patient was treated with antibiotic therapy multiple times, with no clinical benefit.

Periodic fever with symptoms not suggestive of adult-onset Still disease or monogenic fever syndromes such as familial Mediterranean fever (FMF), together with no evidence of cyclic neutropenia or any infectious disease raised the clinical suspicion of PFAPA syndrome. A single dose of prednisolone 60 mg was given at fever onset resulting in rapid symptom resolution. In recent years the patient has experienced a decrease in the periodicity of crises. She is currently crisis-free for over a year.

DISCUSSION

PFAPA syndrome is a chronic disease of unknown aetiology and a common cause of periodic fever in children[1]. It is thought to be caused by inadequate activation of the innate immune system, with no associated infectious or autoimmune triggers. Most patients remit spontaneously before puberty but some may continue to be symptomatic into adolescence[2]. A small subset of individuals has onset of fever in adulthood.

This syndrome 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. In adults, aphthous stomatitis is less frequent and the occurrence of only one of these cardinal manifestations is more common[3]. Adults with PFAPA syndrome may frequently experience atypical symptoms such as nausea, vomiting, myalgia, arthralgia and mild abdominal pain[3].

In children these episodes last an average of 4 days and recur with a clockwork periodicity every 2–8 weeks[2]. However, adult patients may experience longer and less frequent attacks, usually with no clockwork periodicity[3]. Both children and adults are asymptomatic between episodes[2, 3].

During crises, patients usually show moderate leucocytosis and elevation of the erythrocyte sedimentation rate[2] and C-reactive protein levels. Procalcitonin concentrations do not increase proportionally to other acute-phase reactants[4]. The absence of neutropenia immediately before or during episodes helps to differentiate this syndrome from cyclic neutropenia which is another cause of clockwork periodic fever[5].

Establishing the diagnosis of PFAPA syndrome also implies excluding other periodic fever syndromes. FMF is characterized by fever, accompanied by mild to moderate abdominal pain, pleuritis and arthritis. These episodes usually have a shorter duration and occur randomly[1]. Hyper-IgD syndrome may resemble PFAPA syndrome, but episodes are usually accompanied by diarrhoea, generalized lymphadenopathy and high levels of serum IgD[1]. Tumour necrosis factor receptor-associated periodic syndrome (TRAPS) flares usually last longer and are accompanied by periorbital symptoms and migratory rashes[1]. Adult-onset Still disease is characterized by longer periods of fever, prominent arthritis, a salmon-coloured maculopapular skin rash and high levels of serum ferritin. Rapid symptom resolution after a single dose of corticosteroids can also help distinguish PFAPA syndrome from these entities[3].

Patients with PFAPA syndrome usually have no clinical or microbiological evidence of infection. Throat cultures can sometimes yield group A Streptococci which is thought to be considered benign carriage[2] since these patients do not respond to antibiotic therapy. Immunoglobulin and complement levels are usually normal and ANA titres are negative[2].

Usually glucocorticoids are the mainstay choice for episodic therapy, since most patients experience rapid symptom resolution after a single dose of prednisolone 1 mg/kg (or equivalent) given at the onset of fever. As corticosteroid therapy may increase the frequency of episodes[2], some patients may benefit from prophylactic therapy such as cimetidine or even tonsillectomy.

PFAPA syndrome is usually a benign and self-limited disease which resolves with no long-term sequelae. Although rare, it is crucial to differentiate this disease from other causes of periodic fever in adults in order to avoid extensive diagnostic work-up and potentially harmful antibiotic therapy.

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