CASE REPORT

# Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis recurrence temporally associated with allergen-specific immunotherapy in a female adolescent: a case report

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**SUMMARY**

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is the most common periodic fever syndrome in pediatric patients. It is clinically characterized by fever flares lasting 3-7 days, reappearing every 2-8 weeks with a distinctive clockwork regularity. PFAPA generally begins before 5 years of age and usually ceases 3-5 years after onset. Recurrences may be observed in adolescence and adulthood in up to 20% of cases. The authors aim to describe a case of PFAPA recurrence in adolescence temporally associated with allergen-specific immunotherapy (ASIT). A 16-year-old female patient was referred to the rheumatology unit due to recurrent episodes of fever one month after initiating ASIT for allergic rhinitis. These episodes occurred every 4 weeks and lasted 3 days. During these episodes, she also presented with a sore throat, tonsillar exudates, and cervical lymphadenopathy. Abortive treatment with oral prednisolone was attempted in these episodes, with complete resolution of fever after a single dose. After reviewing her medical background, she had previously experienced febrile episodes accompanied by aphthous ulcers and tonsillar exudates occurring every 7-8 weeks from age 2-7. The etiopathogenesis of PFAPA remains uncertain. Environmental triggers, particularly those with immunomodulator effects, may interfere with the immune responses responsible for PFAPA occurrence, but the mechanisms are still unclear. The authors describe the first report of the reappearance of PFAPA flares, possibly due to ASIT. Further studies are needed to fully clarify if ASIT constitutes a true environmental trigger of PFAPA.

***Key words:*** *Autoinflammatory diseases, immunologic desensitization, recurrence, adolescent.*

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## INTRODUCTION

Periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome is the most common periodic fever syndrome in pediatric patients (1). It is clinically characterized by fever flares lasting 3-7 days, reappearing every 2-8 weeks with a distinctive clockwork regularity (1). Patients are usually asymptomatic between attacks, and the most typical manifestations are fever accompanied by at least one of the following: pharyngitis, aphthous ulcers, and/or cervical adenopathy (2, 3). Episodic treatment includes symptomatic management (e.g., non-steroidal anti-inflammatory drugs) and abortive therapy with glucocorticoids (4). Prophylaxis with colchicine has been shown to reduce the number of febrile episodes, and it can be used as a first choice in PFAPA patients or in cases of inadequate response to abortive therapy with glucocorticoids (5). PFAPA generally begins before 5 years of age and usually ceases 3-5 years after onset (2). Complete resolution of PFAPA may also be achieved after tonsillectomy, with high rates of effectiveness (4). Recurrences are not common but may be observed in adolescence and adulthood in up to 20% of cases (1). The authors aim to describe a case of PFAPA recurrence in

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adolescence temporally associated with allergen-specific immunotherapy (ASIT).

## CASE REPORT

A 16-year-old female patient was referred to the pediatric rheumatology unit by her private allergologist due to recurrent episodes of fever one month after initiating ASIT for pollen and mite-induced allergic rhinitis. These episodes occurred every 4 weeks and lasted 3 days, with a temperature maximum recorded at 39.5ºC and little response to paracetamol. During these episodes, she also presented with a sore throat, tonsillar exudates, and cervical lymphadenopathy. On several occasions, a rapid strep test was performed, and it was always negative. She also complained of aphthous ulcers appearing every 2 weeks, which were not necessarily concurrent with febrile episodes. There were no joint, gastrointestinal, ocular, cutaneous, or respiratory complaints. Abortive treatment with oral prednisolone was attempted in these episodes, with complete resolution of fever after a single dose (40 mg).

Bloodwork was performed during a flare and included a complete blood count, liver enzymes, alkaline phosphatase, lactate dehydrogenase, serum immunoglobulins, antinuclear antibodies, antibodies against extractable nuclear antigen, and anti-transglutaminase antibodies, which displayed normal values. However, a marked increase in erythrocyte sedimentation rate [(ESR) 84 mm/hr] and C-reactive protein [(CRP) 45 mg/L] was noticed.

After reviewing her past medical history, she had previously experienced febrile episodes accompanied by aphthous ulcers and tonsillar exudates occurring every 7-8 weeks from age 2 to 7 years. Febrile attacks usually had a spontaneous resolution (although she was occasionally treated with antibiotics), and she was asymptomatic between episodes with normal growth and development. At the time, abortive treatment with glucocorticoids was not attempted. A tonsillectomy had also not been performed. Retrospectively, her episodes were likely attributed to PFAPA syndrome. From 8 to 15 years of age, the patient remained without febrile flares. She only reported occasional mild oral ulcers, without periodicity. She also presented symptoms related to her allergic rhinitis (sneezing, rhinorrhea, and nasal obstruction, with impairment of school performance), which was classified as moderate-severe rhinitis. In her family background, her father also presented frequent episodes of fever and tonsillar exudates during infancy, was treated with penicillin almost every month, and eventually became spontaneously asymptomatic at the age of 5.

In this clinical scenario, we considered the diagnostic hypothesis of a PFAPA recurrence, possibly triggered by ASIT. Therefore, prophylactic therapy with colchicine was initiated since ASIT had an estimated duration of at least 3 years and the patient was improving her allergic symptoms with a significant impact on her quality of life.

She underwent prophylactic therapy for at least 6 months with excellent compliance, and her febrile attacks ceased completely. She maintains aphthous ulcers, but they are less frequent. While afebrile with aphthous ulcers, blood tests displayed normal inflammatory markers (ESR 11 mm/hr, CRP 0.6 mg/L, serum amyloid A protein 0.5 mg/L), and urinary mevalonic acid was normal. Given the clinical course, we considered it unlikely that her symptoms were due to a monogenic periodic fever syndrome, and genetic testing was not pursued.

## DISCUSSION AND CONCLUSIONS

Since 1987, when it was first described by Marshall et al., many hypotheses have been proposed to explain the etiopathogenesis of PFAPA (2). Excluding some papers on the potential contributions of changes in the tonsillar microbiome, many factors against an infectious cause can be pointed out, namely the absence of:

1) a therapeutic response to antibiotics;
2) an epidemiological context during flares; and
3) a predominant infectious agent in microbiological isolates of patients with PFAPA (1).

The lack of significant levels of either autoantibodies or autoreactive T cells contradicts an autoimmune origin (6). For those reasons, and given the excellent response to glucocorticoids, PFAPA has been classified as an autoinflammatory disease.

Unlike the remaining periodic fever syndromes, such as familial Mediterranean fever (FMF), PFAPA does not display a clear monogenic trait (2). In fact, a recent study failed to show a single mutation present in all affected patients by exome sequencing (6). Therefore, current evidence suggests that PFAPA has a polygenic and multifactorial pathophysiology and that it may be caused by immune dysregulation in genetically predisposed individuals after a trigger, which can be environmental (1).

The most consensual hypothesis for etiopathogenesis involves innate and adaptative immune responses (6). Like in other periodic fever syndromes, except for tumor necrosis factor receptor-associated periodic syndrome, an interleukin (IL)-1β dependent innate immune response seems to be the initial step, when an abnormal regulation of the inflammasome may lead to overproduction of proinflammatory cytokines such as IL-1β, IL-6 and IL-18 (1, 6). Inflammasomes can be activated by microorganisms, their metabolic products, or environmental factors (2). This innate dysregulation is then followed by an Th1-type adaptive response, usually seen in autoimmune diseases (6). IL-1β and IL-18 stimulate T cells to secrete interferon γ (IFN-γ), inducing chemokines (CXCL9 and CXCL10) (1). These chemoattractants of T-cells lead to their recruitment to peripheral tissues, which is clinically reflected by tonsillitis and cervical adenitis (6). The absence of elevated levels of gene expression of CXCL13 (chemoattractant for B lymphocytes), as well as the lack of increased T helper (Th) 2- and Th17-cytokines, supports a mainly Th1-type inflammatory response in PFAPA (6, 7).

Studies on environmental triggers responsible for immune responses at the onset or recurrence of PFAPA are lacking in the published literature (2). One case-control study demonstrated that absence or short duration of breastfeeding and maternal smoking (known risk factors for common childhood infections) were more common in children with PFAPA than controls, probably by altering the microbiota of the respiratory tract; ASIT was not studied as a possible risk factor (2). A recent case report described a temporally associated recurrence of PFAPA symptoms with menarche, which had been previously observed in FMF, debating whether hormonal changes may be involved in inflammatory pathways (4). Similarly, a previous case report suggesting a link between ASIT and FMF had been published (8), but there have never been reports correlating PFAPA with ASIT. Autoimmune diseases, namely Sjögren's syndrome, localized scleroderma, recurrent pericarditis, and vasculitis, have also been reported to occur during ASIT (8). On the other hand, a recent review found no evidence of serious adverse effects or disease flare in patients with PFAPA and other systemic autoinflammatory diseases after vaccination (9). This suggests that vaccines, unlike ASIT, don't seem to be an environmental trigger for PFAPA.

ASIT aims to reduce allergic symptoms by providing peripheral T cell tolerance through the induction of T regulatory (Treg) cells. By stimulating Treg cells, Th1-Th2 balance is shifted towards Th1, leading to substantial changes in the cytokine profile of T cells, increasing the synthesis of IL-2, IL-12, IL-18, IFN-γ and tumor necrosis factor-β by Th1 (8). This mechanism has been proposed to explain the association between ASIT and FMF and, considering the Th1-type adaptive response observed in PFAPA, the same logic may be applied to this disease.

In summary, the etiopathogenesis of PFAPA remains uncertain. Environmental triggers, particularly those with immunomodulator effects, may interfere with the immune responses responsible for PFAPA occurrence, but the mechanisms are still unclear. An IL-1β-dependent innate immune response followed by an Th1-type adaptive response appears to be the most consistent pathogenic hypothesis, which could explain why ASIT may be a trigger for PFAPA flares since it shifts Th1-Th2 balance towards the

Th1 response. The authors described the first report of the reappearance of PFAPA flares, possibly due to ASIT. Further studies are needed to fully clarify if ASIT constitutes a true environmental trigger of PFAPA.

**Contributions**
All the authors made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work. C. Granjo Morais and A. Martins contributed equally to this study.

**Conflict of interest**
The authors declare that they have no competing interests, and all authors confirm accuracy.

**Ethics approval and consent to participate**
No ethical committee approval was required.

**Patient consent for publication**
Patient consent was obtained.

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