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Case Report

Late Relapse of Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis (PFAPA) Syndrome: A Case Report

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ABSTRACT

PFAPA syndrome (periodic fever, aphthous stomatitis, pharyngitis, and adenitis) is the most common periodic fever disorder in childhood, typically resolving by early adolescence. Relapse after a prolonged symptom-free interval is rare and has been reported following tonsillectomy-related remission. We describe a 13-year-old girl with intact tonsils who experienced recurrence of PFAPA a decade after initial remission. She presented with a 6-day history of high-grade fever, aphthous ulcers, pharyngitis, and cervical adenitis unresponsive to antibiotics. Investigations showed elevated inflammatory markers, a negative infectious workup, and significant cervical lymphadenopathy on ultrasound. A single dose of prednisolone led to the rapid resolution of symptoms followed by sustained remission on follow-up. This case highlights the diagnostic challenges of late PFAPA relapse and underscores the importance of clinical recognition, exclusion of mimicking conditions, and corticosteroid responsiveness in guiding management.

Key words: Periodic fever, aphthous stomatitis, pharyngitis, adenitis, PFAPA

INTRODUCTION

Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome is the most common periodic fever disorder of childhood. [1] It is classified among the autoinflammatory diseases, which are mediated by innate immune dysregulation rather than autoantibodies or autoreactive T cells. PFAPA usually begins between one and four years of age and is characterized by abrupt-onset febrile episodes lasting 2 to 7 days, recurring every 2 to 8 weeks, with complete wellness in between. [2]

Although it was first described by Marshall et al. in 1987, [3] the pathogenesis remains incompletely understood; both genetic and environmental factors appear to contribute. [4] Familial clustering has been reported, [5] and immunological studies demonstrate abnormal T cell activation and increased pro-inflammatory cytokines during flares.

[4] Tonsillar immune dysregulation is strongly implicated, consistent with the observed therapeutic benefit of tonsillectomy in many cases. [6]

PFAPA is considered a benign condition, with most patients experiencing spontaneous resolution by early adolescence. [7] Nevertheless, persistence into adulthood, adult-onset PFAPA, [8] and relapses after tonsillectomy-related remission have all been documented. [9,10] We present a rare case of adolescent PFAPA relapse after a 10-year remission in a patient with intact tonsils. Awareness of such atypical presentations can prevent unnecessary investigations and guide appropriate, conservative management.

CASE PRESENTATION

A 13-year-old previously healthy girl presented to the emergency department at Sulaiman Al Habib Hospital, Dubai, with a 6-day history of high-grade fever (up to 40°C) associated with malaise, painful cervical swelling, throat pain, aphthous ulcers, and reduced oral intake. She had been treated with oral antibiotics and antipyretics without improvement, prompting further evaluation.

Past medical history revealed recurrent febrile episodes between the ages of 2 and 4 years, accompanied by aphthous ulcers and cervical lymphadenitis. These episodes lasted 5 to 6 days, occurred every 6 to 7 weeks, did not respond to antipyretics or antibiotics, and resolved spontaneously. No definitive diagnosis was established at that time. Family history was unremarkable.

On admission, her weight was 40 kg (25th percentile) and height 153 cm (25th–50th percentile). She was febrile, hemodynamically stable, and mildly dehydrated. Examination revealed enlarged, hyperemic tonsils with whitish exudates, multiple aphthous ulcers on the buccal mucosa, and bilateral tender, mobile cervical lymphadenopathies. No hepatosplenomegaly or other systemic abnormalities were noted.

Laboratory investigations showed hemoglobin 12.3 g/dL, White blood cells (WBC) 13,540/µL with neutrophilic predominance, platelets 253,000/µL, C-Reactive Protein (CRP) 76.5 mg/L, and Erythrocyte Sedimentation rate (ESR) 62 mm/h. Peripheral smear demonstrated neutrophilic leukocytosis consistent with acute inflammation. Serologies for *Epstein–Barr virus* (EBV) and *cytomegalovirus immunoglobulin M* (CMV IgM) were negative. Respiratory viral *polymerase chain reaction* (PCR) panel, blood, throat, and urine cultures were negative. Serum immunoglobulin levels were normal. Stool studies were unremarkable.

Neck ultrasonography revealed enlarged cervical lymph nodes, measuring 3.4 × 1.4 cm on the right and 4.4 × 1.1 cm on the left (**Figures 1** and **2**). Echocardiography was unremarkable.

The patient was treated with a single oral dose of prednisolone (0.5 mg/kg). Within 6 hours, her fever resolved, cervical lymphadenopathy regressed, and her overall condition improved significantly. She was discharged in stable condition. At 1-week follow-up, the aphthous lesions had fully healed. Neck ultrasonography demonstrated marked regression of lymphadenopathy (**Figures 3** and **4**).

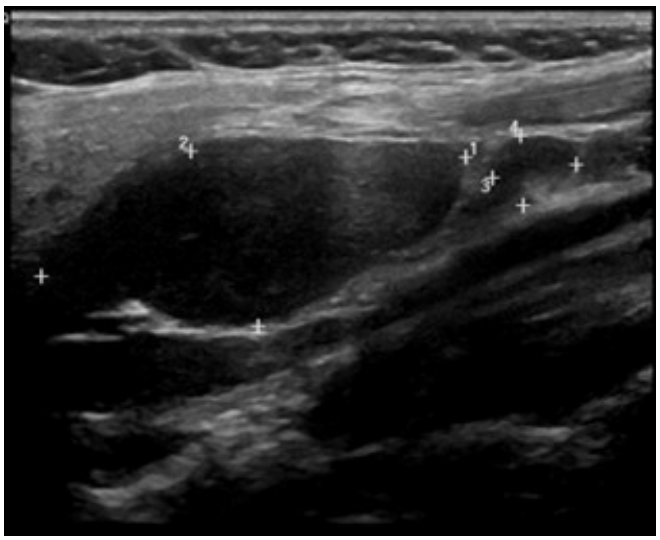

Figure 1: Neck ultrasound before treatment, showing enlarged right cervical lymphadenopathy measuring 3.4 × 1.4 cm.

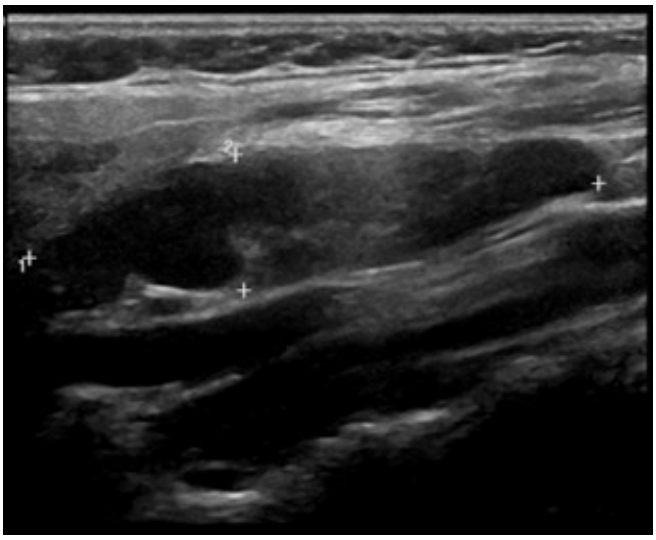

Figure 2: Neck ultrasound before treatment, showing enlarged left cervical lymphadenopathy measuring 4.4 × 1.1 cm.

DISCUSSION

PFAPA syndrome usually begins in early childhood and resolves by adolescence, with only a minority of patients experiencing persistence into adulthood. [8] Relapse after a long symptom-free interval is rare, particularly following a decade of quiescence, as in our case. Reported late recurrences are often linked to prior tonsillectomy, [9,10] making this case—where the tonsils remained intact—clinically noteworthy.

Diagnosing PFAPA syndrome is challenging due to the lack of specific diagnostic markers, the absence of universally accepted criteria, and the necessity to exclude other conditions. [11] In our patient, recognition of the stereotypical fever episodes during early childhood, exclusion of other disorders, and the rapid resolution of symptoms following a single low dose of prednisolone were critical for diagnosis.

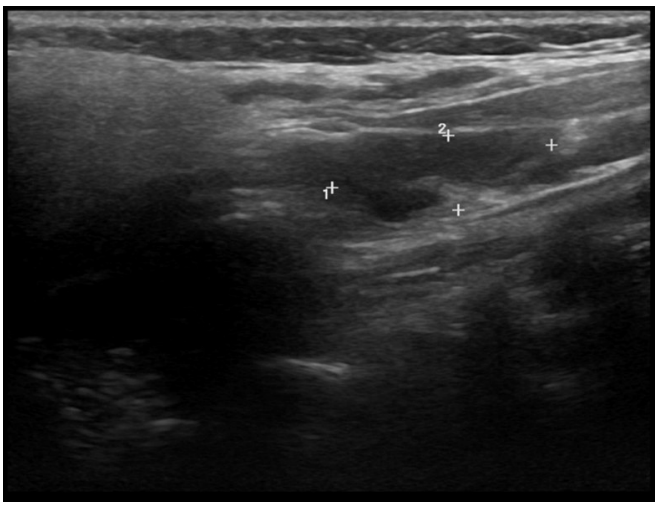

Figure 3: Neck ultrasound after treatment, showing right cervical lymphadenopathy measuring 1.8 × 0.6 cm.

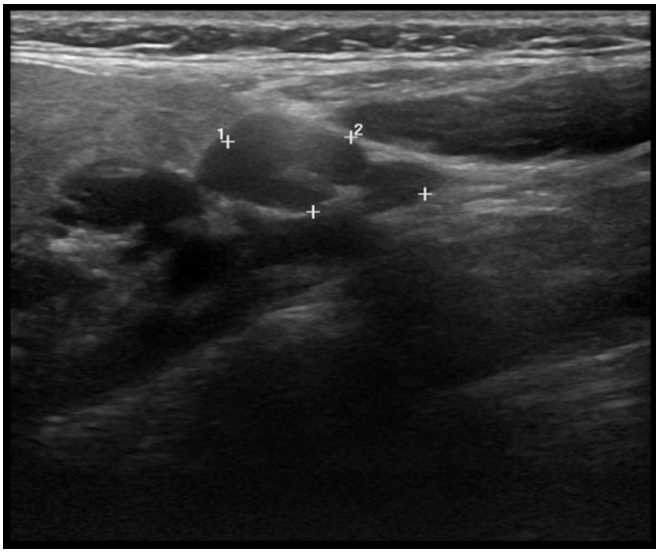

Figure 4: Neck ultrasound after treatment, showing left cervical lymphadenopathy measuring 1.7 × 0.7 cm.

Other periodic fever syndromes, including Familial Mediterranean fever, Mevalonate kinase deficiency, and Behçet disease, were excluded depending on the clinical picture and laboratory results. Viral and bacterial pharyngitis were excluded by negative PCR panels, cultures, and serologies, as well as lack of response to antibiotics.

The literature reports a 4% to 8% co-occurrence of Kawasaki disease (KD) in pediatric patients with PFAPA syndrome. [12] Although KD was initially considered in the differential diagnosis for this patient, it was excluded based on a clinical and laboratory profile more consistent with PFAPA. This diagnosis was further supported by the patient's rapid resolution of symptoms following a single dose of prednisolone and the absence of any clinical or echocardiographic evidence of cardiac involvement.

The mechanism of late relapse remains uncertain. In this patient, reactivation of tonsillar immune pathways is the most plausible explanation. Tonsils harbor activated T cells and antigen-presenting cells that drive cytokine release, and local immune dysregulation may be reinitiated by environmental or internal triggers. Potential contributors include viral infections, bacterial exposure, environmental stressors, and hormonal changes of puberty, which are known to modulate immune responses. [13] The timing of relapse at age 13 suggests that pubertal immunological shifts may have played a role in disease reactivation.

Following the diagnosis, the patient was monitored for one year without further episodes. Given the absence of recurrence, prophylactic therapies such as colchicine or cimetidine were not initiated, and tonsillectomy was not considered. Genetic testing was not pursued, as the clinical picture and corticosteroid response were diagnostic. This case underscores the value of a conservative management approach, avoiding unnecessary interventions while addressing parental concerns.

CONCLUSIONS

This report describes an unusual case of late PFAPA relapse after a decade of remission, underscoring the diagnostic complexity of atypical presentations. Recognition of hallmark clinical features, exclusion of mimicking conditions, and awareness of corticosteroid responsiveness remain essential for accurate diagnosis. Clinicians should be mindful that PFAPA may relapse in adolescence, potentially triggered by pubertal immune modulation or other environmental factors. Careful evaluation can prevent misdiagnosis, avoid unnecessary investigations, and guide appropriate management.

AUTHORS' CONTRIBUTION

All authors have significantly contributed to the work, whether by following the case at the bedside, conducting literature searches, drafting, revising, or critically reviewing the article. They have given their final approval of the version to be published, have agreed with the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

None.

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