

Conjunctivitis as a Sign of PFAPA Syndrome



Dear Editor:

We examined a 9-year-old boy with recurrent aphthae, accompanied with fever (39–41° C), pharyngitis, and adenitis. The duration of episodes was 3 to 5 days, and the child was asymptomatic between episodes. The episodes started 14 months ago and were reiterated at 4-week intervals. In the last 8 to 9 episodes bilateral conjunctivitis was noticed. The patient received nonsteroidal antiinflammatory drugs with or without concomitant antibiotics but did not respond to therapy.

His family history was negative and his development was normal. Intraoral examination revealed pharyngitis and aphthous ulcers (Fig 1 [all figures available at <http://aaojournal.org>]). Palpation demonstrated a painful, bilateral, submandibular lymphadenopathy, and ophthalmologic examination revealed localized painless bilateral mild conjunctivitis (Fig 2).

He was referred to the department of ophthalmology for further investigation. His vision was 20/20 in both eyes, and on the slit-lamp examination no signs of inflammatory cells in the anterior chamber or posterior synechiae were found. The posterior pole and the vessels in the periphery of the fundus were normal.

The patient complained of mild abdominal pain, and his body temperature was 40° C.

Laboratory investigation showed a red blood cell count of $461 \times 10^4/\mu\text{l}$; white blood cell count, $8200/\mu\text{l}$ (neutrophils, 56.2%; lymphocytes, 32.4%; monocytes, 7.1%; eosinophils, 3.9%; basophils, 0.4%); erythrocyte sedimentation rate, 28 mm/hour; and C-reactive protein, 2.2 mg/dl. Electrophoresis of serum proteins showed no abnormalities (Fig 3a). Levels of serum immunoglobulin G (IgG), IgA, and IgM were within normal range (IgG, 1120 mg/dl; IgA, 122 mg/dl; IgM, 119 mg/dl), and immunofixation electrophoresis with anti-IgG, A and D heavy chains, and anti- κ and anti- λ light chains antisera showed absence of monoclonal serum protein (Fig 3b). Serological tests, including Paul-Bunnell, HSV, cytomegalovirus, and Epstein-Barr virus antibodies; rheumatoid latex test; and antinuclear antibodies were negative. Urinalysis was normal, and urine culture was negative. A chest radiograph was normal, and a tuberculin skin test was negative. Blood specimens from the patient and his mother were sent to the Institute of Research in Ophthalmology at Sion, Switzerland. Molecular diagnostics involved the direct sequencing of the tumor necrosis factor receptor 1 (*TNFRSF1A*) gene, known to be associated with tumor necrosis factor receptor-associated periodic syndrome (TRAPS), and revealed no mutation in the exons and adjacent regions of the proband.

A clinical diagnosis of PFAPA (periodic fever, aphthous stomatitis, pharyngitis, and adenitis) syndrome was established. Cimetidine was administered, and the parents reported a slight improvement 6 months later.

PFAPA syndrome is a rare entity.¹ The diagnostic criteria for the typical syndrome are^{2,3}

- usual onset of disease before 5 years of age
- regularly recurring episodes of fever lasting approximately 5 days associated with general symptoms and (1) aphthous stomatitis, pharyngitis, and adenitis in the absence of other signs of upper respiratory infection and (2) acute inflammatory markers
- asymptomatic interval periods of benign long-term course and normal growth parameters
- exclusion of cyclic neutropenia and other episodic syndromes (familial Mediterranean fever, hyper-IgD syndrome, TRAPS)

All the above entities were ruled out in our case. Cyclic neutropenia and hyper-IgD syndrome were excluded by laboratory tests. Familial Mediterranean fever was ruled out by a negative family history, clinical symptomatology, and the fact that in cases of familial Mediterranean fever the febrile episodes are not periodic. In TRAPS, the episodes usually last for more than 1 week, and they are accompanied by myalgias with migratory cutaneous exanthema in more than 80% of the patients. The accompanied conjunctivitis is painful with periorbital swelling. The episodes come about at irregular intervals. TRAPS was ruled out by the laboratory test, as molecular diagnostics involved the direct sequencing of the *TNFRSF1A* gene and revealed no mutation in the exons and adjacent regions of the proband.

In our patient, all diagnostic criteria and laboratory findings were fulfilled except the age of onset. However, there are cases in the literature in which the onset of the syndrome occurred after the age of 5 years.^{4,5}

The clinical features of the syndrome are expressed in varying frequencies. For example, Thomas et al¹ report that aphthae occurred in 77% and nonspecific cutaneous exanthema in 9% of the patients. Conjunctivitis may be a rare clinical manifestation of PFAPA syndrome, and for this reason, it has not been described in the literature until now.

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Figure 1. Multiple herpeslike aphthous ulcers on the lower lip of the patient.

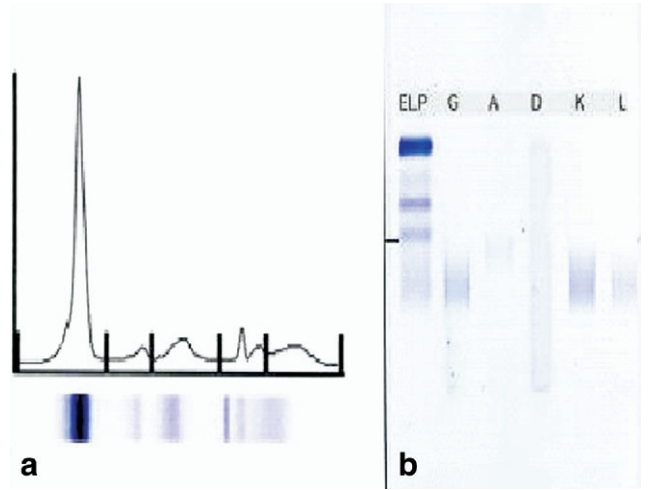


Figure 3. a, Electrophoresis of serum proteins showed no abnormality. b, Immunofixation with anti-immunoglobulin G, A and D heavy chains, and anti- κ and anti- λ light chains antisera showed absence of monoclonal serum protein.



Figure 2. Mild conjunctivitis on both eyes of the child.