

A case of resistant adult-onset periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome responsive to anakinra

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Periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome was originally described by Marshall *et al.* in 1987 and the acronym, PFAPA, was coined two years later along with the diagnostic criteria (1, 2). This clinical entity is characterised by regular occurrences of high fever (>39°C) associated with at least one of the three cardinal clinical signs, aphthous stomatitis, pharyngitis, and cervical adenitis. Additional features, including headache, skin rash, arthralgia and gastrointestinal symptoms, may be present (3). The exact pathogenesis of the disease has yet to be unravelled although an autoinflammatory origin with aberrant cytokine expression has been postulated; cases in members of the same family suggest a possible role of both genetics and the environment (4). PFAPA syndrome usually occurs in young children and arises before the age of 5 (1, 2), although descriptions of cases of adult-onset PFAPA syndrome are on the increase (5, 6). To date, no completely satisfactory treatment options exist. PFAPA is usually responsive to corticosteroids, but their administration may lead to a greatly increased frequency of fever episodes. Tonsillectomy seems to be effective in most children (7) but, on the contrary, seems to be ineffective in adult-onset patients (5, 6). Interleukin (IL)-1 β inhibition recently proved successful in the treatment of resistant PFAPA attacks (8).

Here we report an adult-onset PFAPA patient who was resistant to conventional therapy and was successfully treated with anakinra. In January 2010, a 27-year-old Caucasian male was admitted to our institution for recurrent high-fever attacks, pharyngitis, cervical adenitis, arthralgia and aphthous stomatitis over the previous 3 years. The duration of fever episodes was 4 to 6 days, and the patient reported more than 10 attacks/year. Febrile episodes showed a poor response to non-steroidal anti-inflammatory agents (NSAIDs) and colchicine (1–2 mg/daily). Laboratory analysis showed elevated C-reactive protein (CRP) 4.85 (n.v. <0.5 mg/dl), erythrocyte sedimentation rate (ESR) 96 (n.v. <25 mm/h) and serum amyloid A 652 mg/L (n.v. <10 mg/L). Kidney function and urine sediment were normal. The patient underwent

detailed investigations in order to exclude infectious diseases, autoimmune disorders and underlying malignancies. His family history was not relevant for recurrent fever episodes. The patient's DNA was analysed for mutations in the *MEFV*, *NLRP3*, *MVK* and *TNFRSF1A* genes, responsible for the most common hereditary periodic fever syndromes. No mutations were found. On the basis of Marshall criteria (1, 2) the patient was diagnosed with PFAPA, and treatment with short courses of oral prednisone (on demand) (0.5 mg/kg/daily until resolution of fever attacks) was started. Prednisone promptly brought about the complete resolution of fever episodes, but its administration led to a greatly increased frequency of fever attacks. Tonsillectomy was then performed, leading to an initial partial positive response. However, the fever episodes returned a few months after surgery. Anakinra at a dose of 100 mg daily was then started, and induced a remarkably prompt improvement of symptoms and a rapid decrease of CRP, ESR and SAA concentrations to normal values (checked monthly for 6 months). At the 6-month follow-up, the patient was symptom-free and did not show any sign of disease relapse.

Since it was first described in 1987, PFAPA has generally been considered specific to the pediatric population, however, recent literature has included about 40 cases of PFAPA in adults (5, 6). To date, no completely satisfactory treatment options exist for PFAPA. Corticosteroid therapy of flares is often associated with an increased frequency of attacks, as well as with the side effects of repeated therapy (9). Cimetidine is only effective in about 30% of patients (10). Adenoidectomy and tonsillectomy seems to be an effective treatment strategy for PFAPA children (7), but its role is still controversial, perhaps due to differences reported in cohorts that have been studied (7, 11, 12). The mechanisms responsible for the benefits of adenotonsillectomy are still unknown. Tonsillectomy in adult-onset PFAPA patients seems to be ineffective, as was the case with our patient (5, 6). PFAPA flares are associated with an IL-1 β /IL-18-mediated recruitment of activated T-cells to peripheral tissues, thus implicating IL-1 β as a previously unexplored therapeutic target (8). In our patient, anakinra brought about the complete resolution of fever attacks, thus supporting the hypothesis that in adults, IL-1 inhibition may be an alternative treatment option for resistant PFAPA attacks (5, 6). However, although promising, the results obtained with IL-1 β inhibitors are, to date, limited to very few cases,

and further evaluation in larger cohorts of patients is required. Future randomised treatment trials of patients will help to determine the definite role of anakinra in the management of PFAPA and its long-term benefit and potential adverse effects.

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