**CASE REPORT**

# Periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome, Hodgkin's lymphoma,and the familial Mediterranean fever gene

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## Abstract

The syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenopathy (PFAPA) is a benign, self-limited, auto-inflammatory disorder. The attacks usually start at age 2 to 5 years and cease before the age of 10 years. Affected children grow and develop normally and experience no long-term sequelae.

The course of PFAPA syndrome is attenuated by the carrier state of the familial Mediterranean fever (FMF) gene, MEFV. A high rate of MEFV mutations has also been reported in various hemato-lymphoid neoplasms.

We describe a 19-year-old woman with PFAPA syndrome in remission who was diagnosed with Hodgkin's lymphoma. Although mutations in the FMF gene were not found in this case, the association of PFAPA syndrome with FMF gene mutations and hematological malignancies is discussed.

### Key words

PFAPA syndrome, Hodgkin's lymphoma, Familial Mediterranean fever gene, MEFV mutations

## 1 Background

The syndrome of periodic fever, aphthous stomatitis, pharyngitis, and adenopathy (PFAPA) is a benign, self-limited, auto-inflammatory disorder of the innate immune system. Symptoms include periodic attacks of fever, chills, headache, and musculoskeletal pain accompanied by aphthous ulcers on the lips and buccal mucosa, pharyngitis, and tender cervical adenopathy lasting 3 to 7 days. The attacks usually start at age 2 to 5 years and cease before the age of 10 years; there is a slight male preponderance. The diagnosis of PFAPA syndrome is made on clinical grounds. Glucocorticoids such as prednisone, in doses of 1 to 2 mg/kg orally, dramatically relieve the fever and pharyngitis, usually within hours. This response has even been proposed as a diagnostic criterion for the disease. However, its usefulness is limited by the tendency of prednisone treatment to shorten the interval between attacks in about 25 percent of cases. Between episodes, subjects are healthy, with normal growth and normal laboratory studies. Affected children grow and develop normally and experience no long-term sequelae [1-11].

The course of PFAPA syndrome is attenuated by the carrier state of the familial Mediterranean fever (FMF) gene, MEFV. Carriers of MEFV mutations have shorter attacks that are less likely to occur at regular intervals and a lower prevalence of oral aphthae than patients without mutations [9]. A high rate of MEFV mutations has also been reported in various hemato-lymphoid neoplasms. A study of 46 patients found that multiple myeloma and acute lymphocytic leukemia were associated with a high carrier rate (60% and 33.3%, respectively), whereas chronic lymphocytic leukemia and non-Hodgkin lymphoma were associated with a low carrier rate (9% and 5%, respectively) [12].

The aim of this report was to describe a 19-year-old woman with PFAPA syndrome in remission who was diagnosed with Hodgkin's lymphoma. The association of PFAPA syndrome with FMF gene mutations is discussed.

## 2 Case presentation

A 19-year-old woman presented with painless left cervical swelling of 3 weeks' duration, without fever, night sweats, weight loss, or anorexia. She had been clinically diagnosed with PFAPA syndrome at age 14 years but had been in remission for the last 2 years.

On physical examination, pulse was 73 bpm and regular, and blood pressure was 112/72 mmHg, with no respiratory distress. There were no remarkable findings except for 2 palpable, mobile, non tender masses in the supraclavicular region measuring 2 cm and 0.7 cm in diameter, and splenomegaly. Blood chemistry results were as follows: hemoglobin 11.1g/dl, leukocytes 9000/$mm^3$, platelets 300,000/$mm^3$; glucose, electrolytes, and kidney and liver function tests were within normal range. Lactate dehydrogenase level was 385 u/l (normal 280 u/l). A central mediastinal opacity was noted on chest x-ray. Computed tomography showed ananterior mediastinal mass measuring 8 cm×5 cm. Pathological study of a biopsy sample from the mediastinal mass revealed classical Hodgkin's lymphoma, nodular type.

Analysis for mutations in the FMF gene, including the most common mutations in the Jewish population (M694V, V726A, and E148Q) and in the non-Jewish population (M680I, M694I), as well as exon 10 mutations, yielded negative findings.

## 3 Discussion

We present the first description of Hodgkin's lymphoma in a patient with PFAPA syndrome. Although PFAPA syndrome is believed to be a benign and self-limited disease with no long-term sequelae, an association with malignant diseases, especially hematological neoplasms, is reasonable given its auto-inflammatory nature. This assumption is supported by reports of an association between other chronic inflammatory diseases, such as celiac disease and inflammatory bowel disease, and malignancy [13, 14]. Furthermore, the attacks of PFAPA syndrome are characterized by an elevation in levels of inflammatory cytokines, most notably interferon gamma (IFN-gamma), tumor necrosis factor alpha (TNF-alpha), interleukin (IL)-6, and IL-18. Levels of IFN-gamma-induced cytokines and granulocyte-colony stimulating factor (G-CSF) rise after the onset of fever, whereas IL-7 and IL-17 are suppressed during both febrile and afebrile periods. Even between febrile attacks, levels of some proinflammatory mediators (e.g., IL-1 beta, IL-6, TNF-alpha, and IL-12p70) may be high. Cellular responses might also be involved, as indicated by the rise in thrombocytes levels in the afebrile interval. Furthermore, several studies reported an overexpression of complement IL-1-related and IFN-induced genes during attacks [8, 10, 16, 17].

In the present case, we speculated that the presence of a mutation in the MEFV gene might be the link between the PFAPA syndrome and the Hodgkin's lymphoma. The MEFV gene encodes for proteins that modulate inflammation and cytokine processing. These have found to affect the severity of PFAPA syndrome, giving the disease its attenuated course. At the same time, the proteins have modulatory effects on apoptosis, which may contribute to the oncogenicity of Hodgkin's lymphoma, as reported in other hematological malignancies [12]. However, on genetic analysis, no mutation was found in MEFV in our patient, nor have MEFV mutations been detected in patients with Hodgkin's lymphoma in the past [12]. It is

possible that mutations in genes other than MEFV may be involved in PFAPA syndrome and lead to the expression of hematological malignancies.

Further studies are needed to explore a possible linkage between auto-inflammatory diseases and malignancies, including genetic tracking for specific mutations that might play a role in the two entities.

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