CASE REPORT

A case of adult-onset periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome in Japan

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Abstract
Adult-onset periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome is rare. We report the case of a 23-year-old woman with PFAPA syndrome in Japan. Her symptoms lasted for approximately 5 days in each period regardless of nonsteroidal anti-inflammatory drug or antibiotic treatment. She was diagnosed with PFAPA syndrome based on her periodic self-limiting symptoms and no evidence of other febrile diseases. Following cimetidine therapy, her periodic symptoms diminished. PFAPA syndrome should be considered in patients presenting with periodic fever and upper respiratory symptoms regardless of their age or ethnicity.

KEYWORDS
adult, auto-inflammatory disease, cimetidine, Japanese, periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome

1 | INTRODUCTION

Periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome is an auto-inflammatory disease in which systemic inflammation arises regardless of an infection or autoimmunity. For a long time, this syndrome was recognized as a disease that is unique to the pediatric population; however, dozens of cases of adult-onset PFAPA syndrome have been observed in Europe since the first adult case of this disease was reported in 2008. Although the first case of adult-onset PFAPA syndrome was also already reported, there remains a paucity of data on this syndrome in Japanese adult patients. Here we report a case of adult-onset PFAPA syndrome that showed a good response to cimetidine therapy in Japan.

2 | CASE

A previously healthy 23-year-old Japanese woman presented to the Internal Medicine Department in our hospital after 5 days of fever, sore throat, aphthous stomatitis, and enlargement of the bilateral cervical lymph nodes with tenderness. She experienced similar symptoms 1, 2, and 9 months ago, and in each case, these symptoms lasted for approximately 5 days regardless of therapy with nonsteroidal anti-inflammatory drugs or antibiotics. There was no remarkable family history except for her mother’s neuromyelitis optica. Her menstrual period was regular. She had taken no drugs except for multi-ingredient cold medication prescribed by a local clinic. She had never traveled abroad.

On admission, her body temperature was 37.7°C, and her other vital signs were within the normal ranges. On physical examination, aphthous stomatitis, enlargement of the bilateral submandibular lymph nodes with tenderness, pharyngeal erythema, and enlarged palatine tonsils with white exudates were observed (Figure 1).

Laboratory investigations revealed slightly elevated serum transaminase (aspartate aminotransferase level, 112 IU/L and alanine aminotransferase level, 92 IU/L) and immunoglobulin D (29.1 mg/dL) levels. Bacterial cultures from a throat swab and blood sample showed no growth. Anti-Epstein-Barr virus capsid antigen immunoglobulin G and M titer were order of 160 and under the order of 10. Epstein-Barr virus nuclear antigen was not investigated. Computed tomography revealed enlargement of the bilateral submandibular lymph nodes with no evidence of other abnormal findings. Transthoracic echocardiogram

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revealed no vegetations. The patient refused to undergo genetic examination.

The patient was diagnosed with PFAPA syndrome based on two clinical diagnostic criteria. She satisfied five of six items in Padeh’s diagnosis criteria: monthly cyclic fever in any age group, possible aphthous stomatitis, cervical lymphadenitis, exudative tonsillitis with negative throat culture, completely asymptomatic during intervals, and rapid response to glucocorticoid. She also fulfilled four of five items in Thomas’ criteria: regularly recurring fever under 5 years old; presence of at least one of these symptoms, aphthous stomatitis, cervical adenitis, or pharyngitis, without upper respiratory infection; exclusion of cyclic neutropenia; completely asymptomatic during intervals; normal growth and development. Her diagnosis was confirmed with no evidence of other possible febrile diseases.

After admission, her symptoms recovered within a few days without any treatment. We prescribed cimetidine 800 mg per day to prevent recurrence. Although the aphthous stomatitis and enlarged cervical lymph node appeared a few days per month, none of the other symptoms were observed again. Moreover, the aphthous stomatitis has also stopped occurring 5 months after starting cimetidine therapy (Figure 2).

3 | DISCUSSION

We report a case of adult-onset PFAPA syndrome that responded to cimetidine therapy in Japan. This case suggests that PFAPA syndrome can occur in Japanese adults, and cimetidine therapy may control the disease activity of this syndrome.

More patients, including Japanese patients, are being diagnosed with adult-onset PFAPA syndrome than in the past. Because adult-onset PFAPA syndrome is a new entity that has only been recognized since 2008, the precise prevalence of this syndrome remains unknown. However, a previous study, in which genetic testing was performed on adult patients suspected with autoinflammatory disease, has indicated that there might be a similar number of adult patients with PFAPA syndrome to those with tumor necrosis factor receptor-associated syndrome (TRAPS) or cryopyrin-associated periodic syndromes (CAPS). A similar prevalence of PFAPA syndrome has been observed in another study on adult patients with unexplained recurrent fever. Regarding the prevalence of this syndrome in Japan, a case of adult-onset PFAPA syndrome diagnosed via genetic testing has been reported recently. Following this case, to the best of our knowledge, we report the second Japanese adult patient with PFAPA syndrome. Although large observational studies are needed for confirmation, several reports including ours suggest that adult-onset PFAPA syndrome will be diagnosed more frequently in future, particularly in Japan.
The presentation and therapeutic response of PFAPA syndrome in adult patients seem to be similar to those in pediatric patients. A tendency of a higher prevalence of myalgia and a lower proportion of aphthous stomatitis has been observed in adult patients with PFAPA syndrome compared with that in pediatric patients. However, as almost all adult patients with PFAPA syndrome present with high fever and at least two symbolic symptoms of this syndrome such as aphthous stomatitis, tonsillitis with white exudate, and/or cervical lymphadenopathy at a similar frequency as that seen in pediatric cases, symptoms of PFAPA syndrome may not be different between adult and pediatric cases.\(^2,6\) Regarding Japanese adult cases of PFAPA syndrome, including our case, the patients also presented with high fever and all symbolic symptoms.\(^3\) In terms of therapy, patients with adult-onset PFAPA syndrome showed good response to a single dose of glucocorticoid in Europe.\(^2,6\) In addition, as for our case, therapy with daily oral cimetidine resulted in successful control of disease activity in a former case of a Japanese patient with adult-onset PFAPA syndrome.\(^3\)

Therefore, the diagnostic and therapeutic strategies for PFAPA syndrome in pediatric patients could be adopted in adult patients.

For diagnosis of adult-onset PFAPA syndrome, the clinician must consider several other diseases in the differential diagnosis. A list of hereditary periodic fever syndromes that can develop in adult patients, including familial Mediterranean fever (FMF), TRAPS, CAPS, and hyperimmunoglobulin D syndrome, is shown in Table 1. Four key issues to distinguish PFAPA syndromes from these other autoinflammatory diseases should be borne in mind: clinical symptoms, family history (patterns of inheritance), genetic tests, and response to steroid therapy. In daily practice, the most important differences among these diseases are additional symptoms accompanying recurrent fever. Only patients with PFAPA syndrome present aphthous stomatitis and tonsillitis, while other symptoms such as adenitis and abdominal pain also occur in other diseases. In terms of patterns of inheritance, an autosomal recessive pattern of inheritance may be observed in families of FMF patients, and an autosomal dominant pattern of inheritance may be observed in families of TRAPS and CAPS patients.\(^4\) However, no specific pattern has been reported in PFAPA syndrome. Genetic tests can provide more useful information. Mutations in MEVF, TNFRF1, and NLRP1 are known to be disease-specific findings in FMF, TRAPS, and CAPS, respectively;\(^4\) whereas little is known of the relationship between gene mutations and PFAPA syndrome. If the above information is not helpful or if the clinician does not know the genetic background due to patient’s refusal to undergo genetic tests, such as in our case, a steroid trial during the febrile period may be a possible option for the diagnosis of PFAPA syndrome; even only one 60 mg dose of prednisolone can resolve fever in patients with PFAPA syndrome within a few hours, while other autoinflammatory diseases do not respond immediately.\(^5\) Regarding our case, although a diagnosis of one of the other autoinflammatory diseases discussed above may be possible in this patient because of the lack of genetic investigation and oral steroid trial, the characteristic symptoms and marked response to cimetidine, with no evidence indicating any other diseases, support the diagnosis of PFAPA syndrome.

To date, treatment options for adult-onset PFAPA syndrome are oral steroids, cimetidine therapy, or tonsillectomy.\(^7\) The precise mechanisms of efficacy in these treatments of PFAPA syndrome remain unknown; however, suppression of excessive activation of innate immunity and Th1 cell function seems to play an important role.\(^8\) Overexpression of IL-1-related and interferon-induced genes and Th1 chemokines observed during PFAPA flares may support this theory.\(^9\) Steroid therapy can resolve fever with a high probability; however, side effects and the fact that the interval between fever episodes shortened in 50% of pediatric patients who used prednisolone are great concerns.\(^8\) Tonsillectomy can also provide high efficacy at the expense of safety by invasive procedure.\(^8\) Therefore, although low remission rate was reported (27%) in pediatric patients,\(^8\) we suggest cimetidine therapy as the first-line therapy. Regarding cimetidine dosage, we propose 400–800 mg/day of cimetidine for treatment of adult-onset PFAPA syndrome based on our experience and information from previously reported cases.\(^3\) Further investigations are needed to confirm the response rate to and optimal dose of cimetidine in adult-onset PFAPA syndrome.

### Conclusions

More patients with adult-onset PFAPA syndrome can be detected in Japan, and cimetidine therapy may control this disease activity. Physicians should consider PFAPA syndrome in patients with periodic fever and upper respiratory symptoms irrespective of their age and ethnicity.

### Conflict of Interest

The authors have stated explicitly that there are no conflicts of interest in connection with this article.
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