□ Case Report □

A case of PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome

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PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome is one of the causes of periodic fever in pediatrics with unknown etiology. It is characterized by abrupt onset of fever, malaise, aphthous stomatitis, pharyngitis and cervical adenitis without long-term sequelae. Laboratory findings of this sporadic and nonhereditary syndrome are so non-specific that the diagnosis is based on clinical findings. Oral prednisolone is quite effective in controlling the symptoms. We report a case of a 6-year-old girl who was diagnosed as having PFAPA syndrome after 2 years of episodes, by excluding other disease entities with similar clinical features. The patient was treated with oral prednisolone and her symptoms improved dramatically. **(Korean J Pediatr 2006;49:991-995)**

Key Words : Periodic fever, Aphthous stomatitis, Pharyngitis, Cervical adenitis, Prednisolone

Introduction

Recurrent or periodic fever is fairly common in children[1]. The earliest reports of periodic fever were presented in the 1940s by Reimann[2] and Reimann et al.[3]. Recently, John et al.[1] defined recurrent or periodic fever as three or more episodes of fever within a 6-month period, with no defined medical illness that can explain the fever and with an interval of at least 7 days between febrile episodes. The etiology of recurrent or periodic fever including PFAPA (periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) syndrome varies. PFAPA syndrome is a condition with an unknown etiology and no diagnostic test, and is being increasingly recognized as a cause of recurrent fever[4-6].

In 1987, Marshall et al.[7] reported a previously undescribed periodic fever syndrome of an unknown cause in 12 children. Later, the acronym, PFAPA, was created to define this entity.

Nevertheless, PFAPA is probably an misdiagnosed syndrome due to the difficulty in diagnosis. Ignorance of its benign nature gives rise to unnecessary complementary examinations and unsuccessful treatments.

We present the first case of a pediatric patient in our country diagnosed with PFAPA syndrome after excluding other causes of the periodic fever.

Case Report

A 6-year-old girl was referred to pediatric department of Kangnam St. Mary's hospital with recurrent episodes of high fever that was associated with oral ulcers, a sore throat, tender cervical adenopathy and general body pain. The episodes began at 3 years of age, and there was a 1-2 month period between attacks. She would remain febrile for 3 to 5 days. During the attacks, her fever increased to 39-40°C and the aforementioned symptoms developed. She was completely symptom-free between the attacks. She had never had a rash, joint pain, or any swelling. She had not had any recurrent pyogenic infections. She recovered spontaneously regardless of whether or not antibiotics had been given. She had been hospitalized 10 times with the same complaints. Her prenatal, natal, and postnatal history was unremarkable. She was fully immunized without any adverse reactions and had never suffered serious, life threatening infections. Her developmental milestones were

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normal, and no specific disorder had been diagnosed. Her family history was unremarkable.

A physical examination revealed a body temperature of 38.6°C with her remaining vital signs being within the normal limits. The weight and height were 20 kg (50-75th percentile), and 113 cm (50-75th percentile), respectively, and her general condition was good. There was painful cervical lymphadenopathy, which was 1.5×1 cm in size. There were several ulcers on the mucous membranes of the mouth. The pharynx and tonsils were hyperemic with the remaining physical findings being normal.

A laboratory examination revealed that the hematocrit was 40.5% with a hemoglobin level of 12.9 g/dL; white blood cell count was 24,860/mm^3 with 89% segmented neutrophils, 8% lymphocytes and 2% monocytes; and the platelet count was 215,000/mm^3. The serum electrolytes, renal, and liver function tests were normal. During an attack, the C-reactive protein was 2.7 mg/dL, and the erythrocyte sedimentation rate was 34 mm/h. Urinary analysis was normal. A stool examination for parasites was normal. Numerous culture results of the blood, urine, throat and feces were negative. The peripheral blood smear revealed normal findings.

Investigations during these episodes showed normal levels of C3 and C4 (C3 117 mg/L, C4 29 mg/L, CH50 38.1 U/mL). The serum Immunoglobulin (Ig) showed normal levels of serum Igs (IgG 1160 mg/L, IgA 132 mg/L, IgM 113 mg/L, IgE 48 mg/L, IgD 8U/mL, respectively). The results of the rheumatological tests including the antinuclear antibodies (ANA), anti-DNA antibodies and rheumatoid factor were negative. The CMV IgM and IgG were negative, and the serologic markers of the Epstein-Barr virus; viral capsid antigen (VCA) IgM; VCA IgG; early antigen (EA) DR IgM; Anti EA; Anti Ebstein-Barr nuclear antigen (EBNA) were negative. The toxoplasma IgM and IgG were also negative. The virus culture result of the bone marrow was negative. The cervical lymph node pathology showed paracortical lymphoid hyperplasia (Fig. 1), and the bone marrow biopsy revealed normal hematopoiesis (Fig. 2, 3). The chest X-rays and abdominal ultrasonogram showed normal findings. The neck ultrasonographic finding was

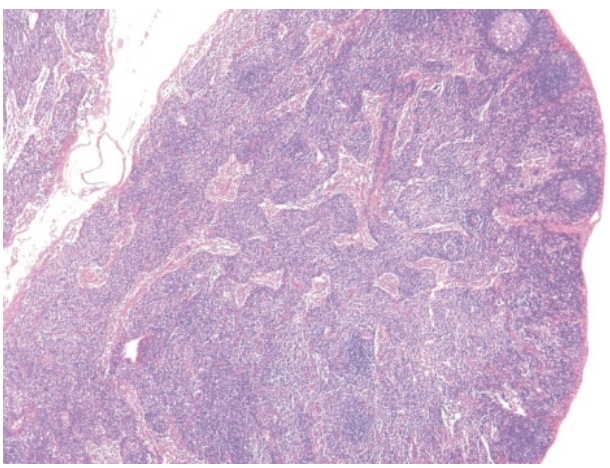

Fig. 1. Lymph node biopsy shows paracortical lymphoid hyperplasia of T zone (hematoxylin and eosin stain, original maginification, ×40).

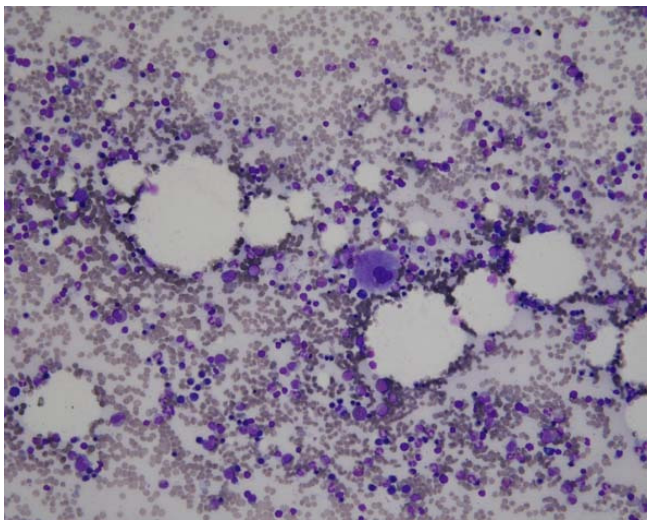

Fig. 2. Bone marrow aspiration reveals normal erythropoiesis, granulopoiesis and megakaryopoiesis (Wright-Giemsa stain, original magnification, ×200).

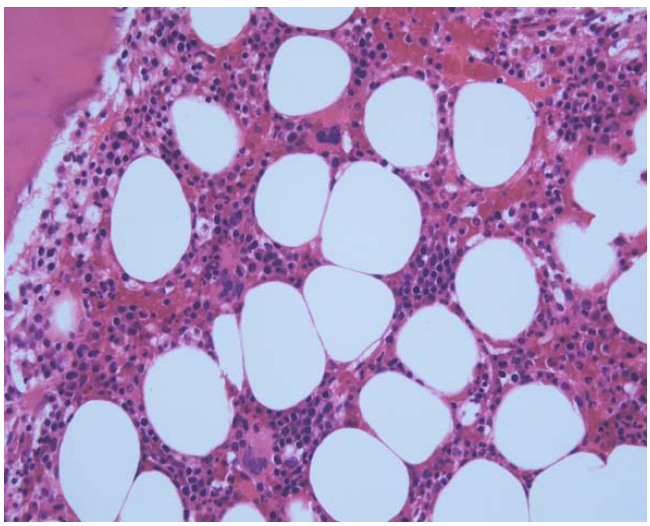

Fig. 3. Bone marrow biopsy reveals variable cellularity (50-80%) with normal hematopoiesis (hematoxylin and eosin stain, original magnification, ×200).

hyperplastic lymph nodes on both spinal accessory chains.

The patient was diagnosed with PFAPA syndrome based on the clinical findings and the exclusion of other diseases. Oral prednisolone (1 mg/kg/day) was prescribed, resulting in a dramatic and complete disappearance of her symptoms.

Forty days later the patient was hospitalized again for the same complaints. Again, a single dose of oral prednisolone was given after the blood, throat and urine culture samples had been obtained. The next day, the patient was free of all symptoms and the cultures were all negative.

As she became older, the frequency of fever and oral ulcers changed from once every 2 months to once every 4-5 months. She has been under follow up and had no symptoms at 7.3 years of age.

Discussion

In 1987, Marshall et al.[7] reported a previously undescribed periodic fever syndrome of an unknown cause in 12 children. Since then, Thomas et al.[4] reported the clinical course, clinical symptoms, and the response to treatment of a long-term follow up of 94 children diagnosed as PFAPA syndrome. The patients presented with febrile episodes that recurred every 3 to 6 weeks. The onset of symptoms began on average at 3 years of age and the fever reached high temperatures (40-41°C), lasting for approximately 5 days. Associated with the fevers were pharyngitis and stomatitis in 67% of cases, and cervical reactive adenopathy in 77% of cases. Other minor symptoms included headache, abdominal pain, nausea, vomiting, chills and malaise. None of these children were immunodeficient. The bacterial, viral, and fungal studies were all negative[4].

The acute episodes were often associated with leukocytosis and a mild increase in the erythrocyte sedimentation rate but no patient showed atypical lymphocytosis or neutropenia. During the asymptomatic intervals, the children were in good health and their growth was normal[7]. The pathogenesis of PFAPA syndrome is unknown. It has been suggested that PFAPA syndrome may be immune-mediated because steroids are an effective therapy[16].

Table 1. Diagnostic Criteria for PFAPA Syndrome

Regularly recurring fevers with an early age of onset (<5 years of age)
Symptoms in the absence of upper respiratory tract infection with at least one of the following clinical signs :
1) aphthous stomatitis
2) cervical lymphadenitis
3) pharyngitis
Exclusion of cyclic neutropenia
Completely asymptomatic interval between episodes
Normal growth and development

Marshall et al., Pediatr Infect Dis J, 1989

A diagnosis of PFAPA syndrome is made clinically and by the exclusion of other conditions. Diagnostic criteria were proposed to identify the disease, and were modified 10 years later[4, 8] (Table 1).

A differential diagnosis should include those entities that appear with an episode of periodic fever. These include cyclic neutropenia, familial Mediterranean fever, hyperglobulinemia D syndrome, Behçet disease and juvenile rheumatoid arthritis[4].

Cyclic neutropenia generally begins within the first year of life[9]. It is characterized by an episode of fever, aphthous ulcers, pharyngitis, lymphadenopathy and neutropenia occurring at intervals of 3 weeks (less than 500/mm^3). Febrile attacks are due to infections, and absolute monocytosis is often present during the febrile period[9]. Neutropenia has never been reported in PFAPA syndrome[9, 10]. Our patient had periodic episode of fever, aphthous ulcer, pharyngitis, and lymphadenopathy, but did not have neutropenia according to repeated laboratory tests.

Familial Mediterranean fever is an autosomal recessive disease that can be easily differentiated from PFAPA syndrome by the family history[11]. It is characterized by periodic acute febrile episodes of short time intervals, usually 2 days, and is associated with arthritis, peritonitis, pleuritis, and rash. Most patients are of Arab, Armenian, Jewish, or Turkish descent, and the onset of the illness generally occurs during childhood[11]. These children do not respond to steroid treatments and experience the insidious development of amyloidosis[11]. In our case, she did not have a family history of recurrent fevers, and she did not have arthritis, peritonitis, pleuritis and skin rash. In addition, her fever lasted for more than 2 days.

Hyperglobulinemia D syndrome is characterized by self-limiting febrile episodes with a variable frequency[12]. The febrile periods usually begin in infancy and might be associated with arthritis, cervical adenitis, chills, headache, macular rash, and splenomegaly[12]. High serum IgD levels (>100 U/ml) are present and are often associated with elevated serum IgA[5, 12]. High levels of mevalonic acid are found in the urine during the febrile attacks[12]. The immu-

noglobulin concentrations in our patient showed a low level of IgD (8 U/mL), and the IgA level was 132 mg/dL, which was within the normal limit for her age. However, the level of mevalonic acid in the urine was not checked.

Behçet disease manifests with aphthous ulcers in the oral cavity that are associated with genital ulcerated lesions, irridocyclitis, skin lesions and synovitis[13]. Furthermore, erythema nodosum, thrombophlebitis, and meningoencephalitis are also observed[13]. The fever usually lasts more than 1 week but it does not show the characteristic periodicity of PFAPA syndrome[13, 14]. Our patient did not have aphthous ulcers. Her findings did not show irridocyclitis, skin lesions, synovitis or the other findings of Behçet disease. Therefore, it was concluded that our patient did not have Behçet disease.

Juvenile rheumatoid arthritis presents with arthritis, fever, hepatosplenomegaly, and systemic adenopathies. The fever lasts several weeks or months, and the onset of the following episode is not predictable. Anemia, morning stiffness, rashes, uveitis, and positive antinuclear antibodies have been observed in some cases[16]. In this case, her fever was periodic, and was not sustained for several weeks or months. The patient did not have arthritis, anemia, uveitis and positive antinuclear antibodies.

All these diseases have peculiar characteristics that allow their diagnosis by means of a positive history and the physical and/or laboratory features.

Treatment with a single dose of prednisolone at the beginning of the symptomatic period relieves the symptoms, even though it does not prevent their recurrence[5]. The response to prednisolone therapy is also a diagnostic clue. Our patient had no fever after being administered prednisolone.

The administration of antibiotics, non-steroidal anti-inflammatory drugs, acyclovir, acetylsalicylic acid, and colchicine are ineffective, except from the reduction of fever induced by anti-inflammatory agents. Tonsillectomy and cimetidine treatment has been associated with remission in some patients[17, 18].

It is well known that typical PFAPA syndrome is benign because the affected children have no long-term sequelae. It generally resolves spontaneously after several years in approximately 40% of patients[4, 5, 18, 19].

In conclusion, typical PFAPA syndrome can be diagnosed easily by detailed history-taking and the physical findings during repeated febrile episodes with tests to rule out other periodic fever syndromes, as mentioned in the literature[4, 17]. Therefore, it is important to recognize this clinical entity in order to avoid unnecessary complementary studies and to improve the therapeutic approach.

한 글 요 약

PFAPA 증후군 1례

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PFAPA 증후군은 소아 시기의 주기성 발열의 원인의 하나로, 급작스럽게 시작되는 발열과 더불어 아프타 구강 궤양, 인두염과 경부 림프절염이 동반되는 것을 특징으로 하는 질환이다. PFAPA 증후군의 원인은 아직 알려져 있지 않으며, 가족력이 없이 산발적으로 발생한다. 또한 검사실 소견에서도 특징적인 소견은 없다. 진단은 임상적인 소견을 바탕으로 이루어지며, 장기적인 합병증을 남기지는 않는다. 현재까지 알려진 치료로는 경구 프레드니솔론이 증상을 조절하는 데 효과적이라고 알려져 있다. 저자들은 2년간의 임상 증상의 반복을 경험하였던 6세 여아에서 다른 질환을 배제한 후 PFAPA 증후군의 진단 요건을 만족하여 경구 프레드니솔론을 사용한 후 증세의 호전을 보인 PFAPA 증후군의 한 예를 보고하고자 한다.

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