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Protracted Febrile Myalgia Associated with Fever of Unknown Origin

Nedeni Bilinmeyen Ateş ile İlişkili Uzamış Febril Miyalji Sendromu

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ABSTRACT

Fever of unknown origin (FUO) is considered in children as fever >38.3°C (101°F) at least once a day for 8 days and more without any apparent diagnosis. There are lots of underlying factors for fever of unknown origin and the three most common etiologic categories in children are infectious diseases, connective tissue diseases, and neoplasms. In this article, we have presented a 15-year-old girl admitted with normal physical, and biochemical examination findings except fever and an elevated acute phase reactant. She was diagnosed with protracted febrile myalgia syndrome (PFMS) when severe myalgia was added to her complaints although she denied previously experienced periodic fever, abdominal pain, arthralgia or chest pain. We presented our case to emphasize that protracted febrile myalgia syndrome, one of the atypical clinical manifestations of Familial Mediterranean fever, may be the presenting symptom of Familial Mediterranean fever as well as an underlying cause of fever of unknown origin.

Keywords: Familial Mediterranean fever, fever of unknown origin, prolonged febrile myalgia

ÖZ

Çocuklarda 8 gün boyunca, günde en az bir kez 38.3°C (101°F)'den yüksek olan ve tetkikler sonucu sebebi bulunamayan ateş yüksekliği, nedeni bilinmeyen ateş olarak adlandırılır. Çocuklarda nedeni bilinmeyen ateşin birçok sebebi vardır ve en sık üç nedeni, enfeksiyon hastalıkları, bağ dokusu hastalıkları ve maligniteleridir. Bu yazıda ateş yüksekliği ve yüksek akut faz reaktanı dışında fizik muayene ve biyokimyasal parametreleri normal sınırlarda olan 15 yaşında bir kız olgu sunuldu. Olgu, karın ağrısı, artralji veya göğüs ağrısı olmadan, ateş şikayetine şiddetli miyalji eklenince, uzamış febrilmiyalji tanısı aldı. Bu olgu, uzamış febril miyalji sendromunun, Ailesel Akdeniz ateşinin ilk semptomu olabileceğini ve nedeni bilinmeyen ateş etiyolojisinde düşünülmesi gerektiğini belirtmek için sunulmuştur.

Anahtar kelimeler: Ailesel Akdeniz ateşi, nedeni bilinmeyen ateş, uzamış febril miyalji

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INTRODUCTION

Fever of unknown origin (FUO) is considered in children as fever >38.3°C (101°F) at least once per day for ≥8 days without any manifest diagnosis.[1] Although familial mediterranean fever (FMF) is generally characterized by episodic fever, protracted febrile myalgia syndrome (PFMS) may be seen as the presenting finding in patients with FMF and may be an etiologic factor for FUO as well.[2,3] The aim of reporting this case was to draw attention to the important characteristics of PFMS, which is an uncommon and severe manifestation of FMF.

CASE REPORT

A 15-year-old girl was admitted to our hospital with a fever of 39.6°C at least twice a day for the last 6 days. She had intermittent fever for the last 4 months despite antibiotic treatment. She was hospitalized for fever of unknown origin, a week ago which responded to meropenem treatment at the end of 8 days. She had no additional symptoms. She had lost 8 kg within the last 10 months. She denied any rash, hair loss, photosensitivity, oral aphthous ulcers or any other complaints. There was no previous history of recurrent fever, chronic illness or familial disorder.

Physical examination revealed a well-developed girl with normal blood pressure and a fever of 38.5°C. Physical examination was normal. Results of urinalysis, hemogram and biochemical tests were within normal limits. C-reactive protein (CRP, 12.3 mg/dL) and erythrocyte sedimentation rate (ESR, 108 mm/h) were elevated. The tests for rheumatoid factor, serological analyses for brucellosis, salmonellosis, toxoplasmosis, hepatitis B and C viruses, Epstein-Barr viruses were negative. Blood, throat, and urine cultures yielded no bacterial growth. Any evidence for active tuberculosis was not detected on chest X-ray and PPD (purified protein derivative) tests. Results of the tests performed to detect antinuclear antibodies, anti-dsDNA, and p/c-anti-neutrophil cytoplasmic antibodies yielded normal results. Titers of mmunoglobulins, and complements were within normal limits Ophthalmologic consultation performed for uveitis, abdominal US (ultrasonography) for intraabdominal infections, and abscesses, neurologic examination and cranial MRI (magnetic resonance imaging) for intracranial abscesses did not revealed any abhormality. Due to fever and weight loss, peripheral smear, bone marrow aspiration and PET were performed to rule out malignancy which could not reveal any malignant disease. Therefore, the patient was accepted as having FUO.

During hospitalization, fever persisted. On the 15th day of her hospital stay, bilateral myalgia affecting both legs was added to the clinical picture and continued for seven days with fever. Fever longer than 72 hours, additional myalgia and high levels of ESR and CRP were suggestive of PFMS and corticosteroid therapy at a dose of 1 mg/kg was instituted. The patient demonstrated a dramatic response, and prompt relief of severe myalgia and fever was achieved. MEFV gene analysis revealed heterozygous P369S, E148Q and K569R variants. Colchicine treatment was also started. ESR and CRP levels regressed to their normal ranges in the first few weeks. Steroid treatment was tapered after the first month and stopped at the end of the second month. No fever or myalgia was observed in the following one and a half-year period.

DISCUSSION

Fever of unknown origin has many causes and the three most common etiologic factors in children are infectious diseases, connective tissue diseases, and neoplasms.[1] Generalized infections that cause FUO are brucellosis, cat-scratch disease, leptospirosis, malaria, mycobacterial infections, salmonellosis, toxoplasmosis, tularemia and viral infections.[3] Bone and joint infections, infective endocarditis, intra-abdominal abscess, hepatic infection, upper respiratory tract infection and urinary tract infection are other infectious causes of FUO.[3] In the present case, there were no features of these diseases in the history, physical examination, laboratory findings and imaging.

Leukemia and lymphoma are the most common malignancies that cause FUO in children.[3] Other

diseases that may cause FUO are Kawasaki disease, cyclic neutropenia, immunodeficiency, inflammatory bowel disease or central nervous system dysfunction. Clinical or laboratory findings are not indicative of these diseases. Rheumatologic diseases are seen in 9% of the cases with FUO and the most common conditions are juvenile idiopathic arthritis (JIA) and systemic lupus erythematosus (SLE). Our patient did not meet the diagnostic criteria for JIA or SLE. Although FMF is in the list of FUO etiology, it is generally characterized by recurrent self-limiting episodes for 1-3 days of fever and painful polyserositis affecting mainly peritoneum, pleura, and synovium.[2,4]

The clinical profile of FMF has been appreciably expanded in the last 10 years as additional features have been described, including PFMS.[4] The symptoms respond effectively to corticosteroids. Myalgia and fever may last for four to six weeks without corticosteroid treatment. A set of clinical diagnostic criteria for PFMS was formulated by Kaplan et al. including obligatory and supporting criteria.[5] Obligatory criteria are: FMF (prior clinical and/or genetic evidence of FMF or familial history), myalgia (symmetric), persistence of myalgia for ≥5 days; and supporting criteria are: at least one M694V mutation, elevated levels of inflammatory markers, and fever>38°C.[5] However, in 33% of the cases, PFMS occurred as the first sign of FMF, and PFMS cases with homozygous E148Q mutation or heterozygous V726A mutation were also reported.[6]

Our case also had symmetrical myalgia for ≥5 days, increased levels of acute phase reactants and fever >38°C. However, there are some striking points in our patient distinguishing her from previous cases reported. To begin with, she presented with persistent fever lasting nearly 3 weeks before the onset of paralyzing myalgia and had intermittent fevers during the last 3 months in addition to weight loss. Therefore, she initially received the diagnosis of FUO. Intermittent fever accompanying weight loss without myalgia made us think about the diagnosis of malignancy and infection at the first time. However, in addition to the symmetrical myalgia, increased acute phase reactans, mutation compatible with FMF and the dramatic response to steroid treatment established the diagnosis of PFMS. As has been reported in the literature the diagnosis of PFMS manifests with different clinical characteristics, only few cases with prolonged severe myalgia without fever were seen. Also abdominal pain with fever was seen prominently at the time of the attack than miyalgia in the literature.[2,7]

Studies have indicated that PFMS is seen more frequently in patients with three mutations: M684V, V726A and E148Q.[8] Although our patient has three different variants in the MEFV gene, K569R has not been defined as a mutation for FMF yet (different from K695R). E148Q mutation seems to be responsible for PFMS in our patient. In conclusion, we reported this case to emphasize that PFMS may be seen in the context of FUO. In patients with FUO and myalgia, PFMS should be kept in mind and genetic analysis may support the diagnosis.

Conflict of Interest: The authors have no conflict of interest.

Informed Consent: The written and verbal consent were taken from the patient.

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