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CASE REPORT

**Alper Soylu · Yeşim Őztürk · Belde Kasap
Nilüfer Akman · Mehmet Türkmen · Salih Kavukçu**

Clinical quiz: A pediatric case presenting with fever and diffuse myalgia

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Abstract Familial Mediterranean fever (FMF) is a multisystem disease characterized by recurrent polyserositis episodes seen in certain ethnic groups. In recent years the clinical picture of FMF has been expanded and severe myalgia is a frequently recognized component of the syndrome. Protracted febrile myalgia syndrome (PFMS), characterized by severe paralyzing myalgia, high fever, abdominal pain, diarrhea, arthritis/arthralgia, and transient vasculitic rashes mimicking Henoch-Schonlein purpura, was first described in patients with FMF in 1994. We describe an 11-year-old Turkish girl with a second attack of PFMS before being diagnosed as having FMF, emphasizing the importance of myalgia for the diagnosis of FMF even in the absence of other symptoms.

Keywords Familial Mediterranean fever · Myalgia · Protracted febrile myalgia syndrome

Introduction

Familial Mediterranean fever (FMF) is a multisystem disease characterized by recurrent polyserositis episodes seen in certain ethnic groups. We describe an 11-year-old Turkish girl with a second attack of PFMS before being diagnosed as having FMF, emphasizing the importance of myalgia for the diagnosis of FMF even in the absence of other symptoms.

A. Soylu · Y. Őztürk · B. Kasap · N. Akman · M. Türkmen
S. Kavukçu (✉)
Department of Pediatrics,
Dokuz Eylül University Medical Faculty,
Inciraltı, Izmir, Turkey
E-mail: s.kavukcu@deu.edu.tr
Tel.: +90-232-2312610

Present address: S. Kavukçu
Mithatpaşa Cad. No: 665/4, 35280 Küçükyalı, İzmir, Turkey

Case report

An 11-year-old girl was admitted to the hospital with fever, malaise, pain in shoulders, and purpuric rashes over both ankles. She had intermittent abdominal pain for 1–2 days 2 weeks previously. Following the relief of abdominal pain, she had severe muscle pain in both thighs and high fever. A few days later, bilateral shoulder pain was added to her complaints. She presented to the emergency department when purpuric rashes developed over her both ankles and pretibial areas. Her past history was characterized by a similar attack 4 years previously. At the age of 7 years she developed purpuric rashes over the ankles and severe generalized muscle pain. She had been hospitalized in a local hospital with the diagnosis of Henoch-Schonlein purpura (HSP). Her complaints were reported to last about 1 month at that time. Family history was nonrevealing.

Physical examination revealed a well-developed girl with normal blood pressure. The temperature was 39°C and there were a few purpuric rashes over both ankles and dorsum of her feet. There was severe tenderness by palpation in both upper arms. The following day she also complained of severe pain in her thighs. This time her upper arms and thighs were so tender that she could not even tolerate touching or walking.

Laboratory analyses were as follows: hemoglobin 11.5 g/dl; white blood cell count 14,000/mm^3; neutrophil 85%; lymphocyte 12%; monocyte 3%; platelet count 486,000/mm^3; total eosinophil 350/mm^3 (normal: <300); glucose 93 mg/dl; urea 15 mg/dl; creatinine 0.5 mg/dl; uric acid 2.1 mg/dl; calcium 9.7 mg/dl; phosphorus 3.8 mg/dl; AST 30 IU/l; ALT 36 IU/l; CPK 22 IU/l; total protein 8.8 g/dl; albumin 3.9 g/dl; and total bilirubin 0.26 mg/dl. Urinalysis was normal. C-reactive protein (CRP; 238 mg/l, normal: <5 mg/l) and erythrocyte sedimentation rate (ESR; 83 mm/h) were elevated. Rheumatoid factor was normal (10 u/ml, normal: 0–14). Chest X-ray and abdominal ultrasonography, including Doppler examination of liver and kidney, were normal.

Serology for brucellosis, salmonellosis, toxoplasmosis, trichinellosis, HBV, HCV, and CMV was negative. Blood and urine cultures were sterile. Occult blood in stool was negative. C3 (208 mg/dl, normal: 90–180 mg/dl) was increased and C4 (24 mg/dl, normal: 10–40 mg/dl) was normal. ANA, anti-dsDNA, p-ANCA, and c-ANCA were negative. IgG was 2546 mg/dl (normal: 700–1600 mg/dl), IgA 473 mg/dl (normal: 70–400 mg/dl), IgM 219 mg/dl (normal: 40–230 mg/dl), and IgE 99 IU/ml (normal: 0–200 IU/ml). Ophthalmologic consultation and electromyography were normal.

Questions

The following questions are put forward:

1. What is your clinical diagnosis and what simple approach do you perform to support this diagnosis?
2. How do you confirm the diagnosis?

Answers

The following answers are given:

1. The clinical picture of fever, skin lesions resembling Henoch-Schonlein purpura, and severe long-standing myalgia nonresponsive to nonsteroidal antiinflammatory drugs with normal serum CPK, normal EMG, hyperglobulinemia, and increased CRP are in favor of protracted febrile myalgia syndrome (PFMS), which is a clinical feature of familial Mediterranean fever (FMF) [1]. Myalgia and fever in PFMS improve within 2 days with steroid treatment; thus, we started prednisolone 2 mg/kg day^{-1} and the symptoms disappeared within 2 h, supporting the diagnosis of PFMS.
2. PFMS may appear during the course of apparent FMF or it may precede the other clinical features of FMF [2]. In the first case the diagnosis is obvious; in the latter, the presence of FMF in the family history may be helpful. No FMF case was present in our patient's family and her parents were not relatives; however, description of a similar attack 4 years previously helped us in the diagnosis of PFMS and FMF.

Confirmation of FMF is based on some clinical criteria [3]. Our patient did not fulfill the criteria for the clinical diagnosis of FMF. On the other hand, genetic diagnosis has been possible since 1997 in this autosomal-recessive disease [4]. Since the clinical findings and response to steroid therapy supported the diagnosis of PFMS, which is a clinical feature of FMF, we performed genetic analysis for FMF and showed that the patient was homozygous for M694 V mutation. Since this mutation is highly associated with amyloidosis, we started colchicine treatment as well, even though the clinical findings of the patient did not meet the criteria for FMF [5].

Discussion

Prolonged fever, severe extremity pain, and elevated acute phase reactants could be associated with malignancy, especially hematologic malignancies. Our patient's hematologic evaluation revealed normal hemoglobin and platelet count, and leukocytosis with polymorphonuclear predominance. There was no atypical cell in peripheral smear. Weight loss, anorexia, hepatosplenomegaly, or lymphadenopathy were not present. In addition, there was a similar attack 4 years previously excluding the possibility of malignancy in this patient.

Fever, rash, myalgia, and elevated ESR could be due to a variety of diseases such as polyarteritis nodosa (PAN), dermatomyositis (DM), and systemic lupus erythematosus (SLE). Dermatomyositis was excluded on the basis of normal CPK, and clinical and EMG findings [6]. Serologic findings were against the SLE. Polyarteritis nodosa was the first probable diagnosis in our patient; however, there was no sign of renal involvement, ANCA was negative, and no visceral vascular aneurysm was detected; thus, no histopathologic or radiologic sign of vascular inflammation required for the diagnosis of PAN was present [7]. Henoch-Schonlein purpura was another diagnostic possibility, but absence of typical rash, history of a similar attack previously, and very high levels of ESR and CRP were not compatible with HSP.

Familial Mediterranean fever is a genetic multisystem disease characterized by recurrent self-limiting painful episodes of sterile peritonitis, pleuritis, and arthritis. Certain ethnic groups, including Turks, Armenians, Arabs, and Jews, have a predisposition to the disease. There are more than one set of diagnostic criteria for FMF including those of Heller et al. and Livneh et al. [4, 8]. These include mainly clinical criteria and are mostly based on recurrent fever and polyserositis episodes including peritoneal, pleural, and joint spaces; however, the clinical picture of FMF has been expanded appreciably during the past 15 years and additional clinical features, including severe myalgia, scrotal swelling, and cardiac involvement, have been described [3]. Only the criteria of Livneh et al. include exertional leg pain as a minor criterion [4].

Myalgia as an associated finding of FMF was first described by Schwabe and Peters in 1974 in two Armenians. It was first addressed as a feature of FMF in 1981 [2]. Protracted febrile myalgia syndrome (PFMS) was described in patients with FMF by Langevitz et al. in 1994 [1]. Increasing knowledge about FMF myalgia led Livneh et al. to consider exercise-induced myalgia as one of the minor diagnostic criteria [4].

Majeed et al. studied the incidence and clinical patterns of myalgia prospectively in a group of 264 children with FMF and found the incidence of myalgia as 25%

[2]. They defined myalgia as pain or tenderness, or both, in the extremities away from the joints in the absence of joint swelling and signs of underlying osteomyelitis. The FMF myalgia is classified into three groups: exercise-induced myalgia (onset of sever myalgia within 8 h of execise that lasts for 1–3 days), spontaneous myalgia (mild to moderate myalgia not related to exercise or any other precipitating factor that lasts for about 8 h), and the PFMS that comprised 11% of all cases of myalgia [2, 3]. The PFMS is characterized by severe paralyzing myalgia and high fever, sometimes accompanied by abdominal pain, diarrhea, and arthritis/arthralgia, and in a few patients by transient vasculitic purpura mimicking HSP. The episode lasts for 4–6 weeks, except in those patients treated with corticosteroids. High ESR, hyperglobulinemia, normal CPK, and subtle nonspecific inflammatory myopathic changes on EMG are the other characteristics [1, 2]. The previous attack of our patient was reported to last about 4–5 weeks. She was not treated with steroids at that time; however, the present episode lasted about 2 weeks, and when prednisolone was started the symptoms abated within 2 h. In addition to response to steroids, all the clinical and laboratory findings of our patient were compatible with the PFMS. The mean ages at onset of FMF and myalgia were reported to be 5.2 and 7 years, respectively [3]; however, it was also reported that the PFMS may precede the diagnosis of FMF. The PFMS may recur even under the colchicine prophylaxis [2]. Our patient was 7 years of age during the first attack. Although she had a second attack of PFMS, she still did not have any other symptom of FMF.

This case emphasizes the importance of myalgia in general and the PFMS in particular for the diagnosis of FMF even in the absence of other symptoms or family history of FMF.

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