İzmir Dr. Behçet Uz Çocuk Hast. Dergisi 2013; 3(3):207-210
doi:10.5222/buchd.2013.207

Olgu Sunumu

Concurrence of protracted febrile myalgia syndrome and *Mycoplasma pneumoniae* infection: Case report

Uzamış febril myalji sendromu ve *Mycoplasma pneumoniae* enfeksiyonu birlikteliği: Olgu sunumu

Demet ALAYGUT[1], Suar ÇAKI KILIÇ[2], Hazım Alper GÜRSU[3]

[1]*Cumhuriyet Üniversitesi Tıp Fakültesi, Çocuk Nefroloji Bilim Dalı, Sivas*
[2]*Cumhuriyet Üniversitesi Tıp Fakültesi, Çocuk Hematoloji Bilim Dalı, Sivas*
[3]*Sivas Numune Hastanesi, Pediatrik Kardiyoloji Bölümü, Sivas*

ABSTRACT

Familial Mediterranean Fever (FMF) is characterized by recurrent attacks of inflammation in predominantly serosal and synovial membranes, is caused by MEFV gene mutations resulting in the emergence of abnormal pyrin production. Protracted febrile myalgia syndrome (PFMS), a kind of vasculitis requiring corticosteroid treatment, is associated with M694V mutation of MEFV gene. Patients with FMF are susceptible to certain antigens, some of which cause mild stimulation of immune response leading to typical FMF attack. Here we report a case where the patient developed PFMS with FMF concurrently with atypical pneumoniae secondary to *Mycoplasma pneumoniae*. Mycoplasma pneumoniae-associated cytokine release may be a predisposing or triggering factor for FMF and we aimed to discuss the possible mechanisms of concomitant *M.pneumonia* infection and FMF-associated PFMS.

Key words: protracted febrile myalgia syndrome, Mycoplasma pneumoniae, child, familial Mediterranean fever

ÖZET

Ailesel Akdeniz Ateşi (AAA), belirgin olarak serozal ve sinoviyal membranlarda tekrarlayıcı inflamasyon atakları ile karakterize, MEFV gen mutasyonu sonucu anormal pirin proteininin ortaya çıkması ile karakterize bir hastalıktır. Uzamış febril myalji sendromu (UFMS) ise steroid tedavisi gerektiren bir tür vaskülit olup MEFV geninde ortaya çıkan M694V mutasyonu ile ilişkilidir. AAA'lı hastalar, AAA'nın tipik atakların başlamasına neden olan ve hafif immunolojik stimulasyon yapan bazı antijenlere karşı duyarlıdır. Bu yazıda AAA tanısı ile takip edilen ve *M. pneumoniae* enfeksiyonuna sekonder atipik pnömoni geçiren bir hastada ortaya çıkan UFMS tablosu rapor edilmiştir. *Mycoplasma pneumoniae* ile ilişkili sitokin salınımının AAA ile ilişkili UFMS'nun ortaya çıkışında tetikleyici olabileceği vurgulanmak istenmiştir.

Anahtar kelimeler: uzamış febril myalji sendromu, *Mycoplasma pneumoniae*, çocuk, Ailesel akdeniz ateşi

Alındığı tarih: 24.05.2013
Kabul tarihi: 04.11.2013

Yazışma adresi: Yard. Doç. Dr. Demet Alaygut, Cumhuriyet Üniversitesi Tıp Fakültesi Çocuk Nefroloji Bilim Dalı, 58140-Sivas
e-mail: demetalaygut@yahoo.com

INTRODUCTION

Familial Mediterranean Fever (FMF) is the most frequent periodic syndrome characterized by recurrent, acute, self-limiting episodes of fever accompanied by polyserositis commonly observed in certain ethnic groups with Jewish, Arabic, Turkish, and Armenian ancestry [1,2]. In recent years, other clinical features of FMF have been recognized, including severe myalgia [3]. Protracted febrile myalgia syndro-

me (PFMS), which was first described in patients with FMF in 1994, is a vasculitic pathology resulting in severe paralyzing usually symmetric, bilateral myalgia involving lower extremities, associated with high fever, abdominal pain, diarrhea, arthritis/arthralgia, transient vasculitic rashes mimicking Henoch-Schonlein purpura (HSP), elevated levels of inflammatory markers, normal creatine phosphokinase (CPK) levels, and non-specific changes on electromyograms (EMG) [4]. Association of *M. pneumoniae* infection and FMF is very rare and only a single study investigating this association have been cited in the literature [5]. Here, we describe an FMF patient presenting with PFMS at the time of *M. pneumoniae* infection. To our knowledge, this is the first reported case having all these characteristic features simultaneously. We have discussed the possible mechanisms leading to simultaneous *M. pneumoniae* infection and FMF-associated PFMS.

CASE REPORT

A 12-year-old boy presented with fever (39.1°C), cough and severe pain in his shoulders, arms, and neck. His complaints had begun 2 weeks ago only as coughing. A few days later abdominal pain and fever were added to his complaints. He had been evaluated in a local healthcare facility, and hospitalized with a diagnosis of pneumonia. One week later he had complained of severe pain in his shoulders, arms, neck and legs and inability to walk. His medical history was marked by the diagnosis of Familial Mediterranean fever one year ago, because he had abdominal pain attacks with fever every 3 to 4 months for the last 2 years, and he were using colchicine therapy (1 mg/day). Mutational analysis of MEFV gene was homozygous for M694V. His parents were not relatives, and her family history was nonrevealing.

Physical examination revealed normal anthropometric development, fever (38.4°C), tachycardia, normal blood pressure, and severe muscular tenderness over the arms, neck, and shoulders. There was a 1/6 systolic murmur over the apex on cardiac auscultation. The rest of the physical examination was normal.

Laboratory test results were as follows: hemoglobin 12.8 g/dL; white blood cell count 11.700/mm^3; neutrophil 85%; lymphocyte 12%; monocyte 3%; platelet count 342.000/mm^3; glucose 96 mg/dL; urea 9 mg/dL; creatinine 0.35 mg/dL; uric acid 2.5 mg/dL; calcium 9.2 mg/dL; phosphorus 4.9 mg/dL; AST 25 IU/L; ALT 22 IU/L; CPK 43 IU/L; total protein 7.4 g/dL; albumin 3.9 g/dL; and total bilirubin 0.26 mg/dL. Urinalysis was unremarkable. C-reactive protein (CRP; 121 mg/L, normal: <5 mg/L) and erythrocyte sedimentation rate (ESR; 93 mm/h) were elevated. Chest X-ray and abdominal ultrasonography, including Doppler examination of liver and kidney were normal. Serologic test results for brucellosis, salmonellosis, toxoplasmosis, HBV, HCV, and CMV were negative. Only Mycoplasma pneumoniae (*M. Pneumoniae*) IgM antibodies were positive. Blood and urine cultures were sterile. ANA, anti-dsDNA, p-ANCA, and c-ANCA were negative. IgG was 2675 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). Electromyographic examination results, and C3 and C4 levels were normal. ASO titer was elevated (3760 IU/mL). Bone marrow aspiration was consistent with inflammation-associated depression in erythroid series. Atypic cells were not seen. Echocardiographic examination was not remarkable.

He was diagnosed as PFMS, and responded rapidly to 2 mg/kg prednisolone administered every 24 hours. For the *M.pneumoniae* infection, Chlaritromycin therapy was initiated. His myalgia and febrile symptoms resolved within 24 hours. In addition, acute-phase reactants declined rapidly.

DISCUSSION

Protracted febrile myalgia syndrome is characteri-

zed 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 Henoch-Schonlein purpura (HSP). It is a clinical feature of FMF [6]. 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 other characteristic findings [6,7].

Diagnosis of PFMS in our patient was considered based on the clinical signs, presence of high levels of acute phase reactants, normal CPK, and past medical history.

Vasculitic complication has been reported with FMF. Approximately 5% of the individuals with FMF have been reported to have HSP and about 1% have polyarteritis nodosa (PAN). Protracted febrile myalgia is another vasculitis-associated clinical entity among patients with FMF [8]. Pathogenesis of FMF is related to exaggerated inflammation secondary to abnormal pyrin that is unable to downregulate the inflammatory response [3]. During an FMF attack, consumption of circulating immune complexes, hypergammaglobulinemia, and complement component are detected, and these return to their normal levels between attacks [8]. Previous studies have reported that diseases with vasculitic components like HSP, PAN, and acute rheumatic fever (ARF), which can be seen after streptococcal infections, are encountered with a higher frequency in patients with FMF [9]. Patients with FMF with vasculitis have high titers of antistreptolysin O (ASO). Thus, it has been suggested that there could be a relation between vasculitis and streptococcal infections in FMF [8]. Our patient had also a high titer ASO. Patients with FMF might demonstrate an abnormally exaggerated response to streptococci [10]. Increased ASO titers in these patients indicate that streptococci could be one of the agents inducing PFMS in patients with FMF. Yalçınkaya et al demonstrated that individuals with FMF frequently have high ASO and anti-DNAse B levels, even in the absence of recent streptococcal pharyngitis. They explained this reaction with two possible mechanisms. One of them was that elevated anti-streptococcal antibody titers may persist longer and may not even return to normal levels in patients with FMF. The second mechanism was that there might have been patients with unrecognised streptococcal throat infection in the last 4 months and carry a risk for non-suppurative complications [10]. Despite all these attempts, triggering factors of FMF attacks have not been studied well. Karadag O et al reported that infections were one of the triggering factors for the attacs in patients with FMF [11].

Mycoplasma pneumoniae is a common intracellular pathogen, which is responsible for infections of the respiratory tract, particularly in pediatric age. Nevertheless, there is an increasing evidence that *M. pneumoniae* plays a role in determining clinical presentations different from the respiratory ones [12]. Two types of complications were observed with *M. pneumonia*. The first type was due to an invasion of the tissue and the second type was mediated by an autoimmune mechanism [13]. In our case we thought that this agent is responsible for FMF attacks. In countries like ours, where FMF is prevalent with a carrier incidence of 1/3-1/5, coexistence of a common childhood disease is frequently seen [14]. *M. pneumoniae* infection may be coincidental too. However, ours is the first report of a child with PFMS and *M. pneumoniae* infection. The ability of *M. pneumoniae* to induce proinflammatory cytokines has been well documented over the years, and these cytokines are suggested to play an important role in the pathogenesis of particularly chronic *M. pneumoniae* infections. It has been demonstrated that *M. pneumoniae* infections provoke elevation of oxidative stress, and proinflammatory cytokines including tumor necrosis factor (TNF)-α, IL-6, IL-8, and IL-1β. Infection with *M. pneumoniae* causes a rapid and strong induction of IL-1β gene expression [15]. In FMF and associated vasculitic diseases like PFMS, pathogenesis is also related to exaggerated inflammatory response to various triggers

due to decreased inhibitory function of mutated protein pyrin (also called marenostrin) characterized by high levels of TNF-α, IL-6, IL-8, and IL-1β (16). These proinflammatory cytokines may cause endothelial cell dysfunction, which is followed by endothelial damage, leukocyte infiltration, and fibrinoid necrosis within the arterial wall leading to vasculitis [16]. In our patient, proinflammatory cytokines expressed due to *M. pneumoniae* infection might have triggered an exaggerated inflammation leading to FMF-associated PFMS period.

In conclusion, we have reported the first case presenting with FMF-associated PFMS concurrent with *M. pneumoniae* infection. PFMS is a rare but severe manifestation of FMF and has different features, one of which is paralyzing muscle pain. Myalgia does not improve unless the patient is treated by steroids, and rapid response to short courses of corticosteroids may also confirm the diagnosis of PFMS. Presence of *M. pneumoniae* infection with PFMS in our patient suggests that *M. pneumoniae* associated cytokine release may be a predisposing or a triggering factor for FMF-associated PFMS. PFMS should be considered in the presence of suggestive findings in patients with *M. pneumonia* infection.

REFERENCES

1. Livneh A, Langevitz P, Zemer D, Zaks N, Kees S, Lidar T, Migdal A, Padeh S, Pras M. Criteria for the diagnosis of familial Mediterranean fever. *Arthritis Rheum* 1997;40:1879-1885. http://dx.doi.org/10.1002/art.1780401023 PMid:9336425
2. Bakkaloglu A. Familial Mediterranean fever. *Pediatr Nephrol* 2003;18:853-859. http://dx.doi.org/10.1007/s00467-003-1185-2 PMid:12836090
3. Soylu A, Kasap B, Turkmen M, Saylam GS, Kavukcu S. Febrile myalgia syndrome in familial Mediterranean fever. *J Clin Rheumatol* 2006;12:93-96. http://dx.doi.org/10.1097/01.rhu.0000208635.64537.10 PMid:16601545
4. Kaplan E, Mukamel M, Barash J, Brik R, Padeh S, Berkun Y, Uziel Y, Tauber T, Amir J, Harel L. Protracted febrile myalgia in children and young adults with familial Mediterranean fever: analysis of 15 patients and suggested criteria for working diagnosis. *Clin Exp Rheumatol* 2007;25:S114-117. PMid:17949564 PMid: 14665940
5. Somekh E, Gorenstein A, Serour F. Acute epididymitis in boys: evidence of a post-infectious etiology. *J Urol* 2004;171(1):391-4. http://dx.doi.org/10.1097/01.ju.0000102160.55494.1f PMid:14665940
6. Langevitz P, Zemer D, Livneh A, Shemer J, Pras M. Protracted myalgia syndrome in patients with familial Mediterranean fever. *J Rheumatol* 1994;21:1708-1709. PMid:7799354 PMid: 15889305 PMid: 10709887
7. Soylu A, Oztürk Y, Kasap B, Akman N, Turkmen M, Kavukcu S. Clinical quiz: A pediatric case presenting with fever and diffuse myalgia. *Rheumatol Int* 2005;25:314-316. http://dx.doi.org/10.1007/s00296-004-0530-5 PMid:15889305
8. Tekin M, Yalcınkaya F,Tumer N, Akar N, Mısırlıoğlu M, Cakar N Clinical, laboratory and molecular characteristics of children with Familial Mediterranean Fever-associated vasculitis. *Acta Paediatr* 2000;89:177-82. http://dx.doi.org/10.1111/j.1651-2227.2000.tb01212.x
9. Ozdogan H, Arisoy N, Kasapçapur O, Sever L, Calişkan S, Tuzuner N, Mat C, Yazici H. Vasculitis in familial Mediterranean fever. *J Rheumatol* 1997;24:323-327. PMid:9034991 PMid: 12223985 PMid: 22814791
10. Yalçinkaya F, Ince E, Uçar T, Ozkaya N, Tekin M, Elhan AH, Tutar E, Güriz DH, Aysev D, Gökdemir R, Doğru U, Tümer N. Antistreptococcal response is exaggerated in children with familial Mediterranean fever. *Clin Rheumatol* 2002;21:378-381. http://dx.doi.org/10.1007/s100670200101 PMid:12223985
11. Karadag O, Tufan A, Yazisiz V, Ureten K, Yilmaz S, Cinar M, Akdogan A, Erdem H, Ozturk MA, Pay S, Dinc A. The factors considered as trigger for the attacks in patients with familial Mediterranean fever. *Rheumatol Int* 2013;33(4):893-7. http://dx.doi.org/10.1007/s00296-012-2453-x PMid:22814791
12. De Donno V, La Dolcetta M, Fissore MF, Benech P, Peduto A, Maddaluno S, Alpicrovi C, Chiossi M. Mycoplasma pneumoniae is not a respiratory pathogen only: two case reports of "atypical" clinical presentations. *Minerva Pediatr* 2008;60(1):135-9. PMid:18277372
13. Balasco Patino F, Perez Maestu R, Lopez de Letona JM. Mechanisms of disease in Mycoplasma pneumoniae infection. Clinical manifestations and complications. *Rev Clin Esp* 2004;204(7):365-8. PMid:15274782
14. Baş F, Kabataş-Eryilmaz S, Günöz H, Darendeliler F, Küçükemre B, Bundak R, Saka N. Type 1 diabetes mellitus associated with autoimmune thyroid disease, celiac disease and Familial Mediterranean fever: case report. *Turk J Pediatr* 2009;51:183. PMid:19480334
15. Yang J, Hooper WC, Phillips DJ, Talkington DF. Interleukin-1 beta responses to Mycoplasma pneumoniae infection are cell-type specific. *Microb Pathog* 2003;34(1):17-25. http://dx.doi.org/10.1016/S0882-4010(02)00190-0
16. Aksu K, Keser G. Coexistence of vasculitides with familial Mediterranean fever. *Rheumatol Int* 2011;31:1263-1274. http://dx.doi.org/10.1007/s00296-011-1840-z PMid:21547384