Case Report / *Olgu Sunumu*

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Co-existance of Juvenil Ankylosing Spondylitis with Familial Mediterranean Fever and Takayasu's Arteritis: A Case Report

Juvenil Ankilozan Spondilit, Ailesel Akdeniz Ateşi ve Takayasu Arteriti Birlikteliği: Bir Olgu Sunumu

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Abstract

Juvenile ankylosing spondylitis (JAS) coexisting with Familial Mediterranean Fever (FMF) or Takayusu's arteritis (TA) together with JAS have been reported in the literature. However, co-existance of these three diseases has not been reported yet. Here, we present a 17-year- old female patient presenting with JAS who was subsequently diagnosed with FMF and TA. To the best of our knowledge, this is the first case of JAS presenting with FMF and TA.

Keywords: Juvenil ankylosing spondylitis, Familial Mediterranean Fever, Takayasu's arteritis, pediatric

Öz

Literatürde Ailesel Akdeniz ateşi (AAA) ve JAS, Takayasu arteriti (TA) ve JAS birlikteliği daha önce bildirilmiştir. Bilgilerimize göre şimdiye kadar bu üç hastalığın birlikteliği daha önce bildirilmemiştir. Burada JAS tanılı 17 yaş kadın olguda tesadüfen saptanan AAA ve TA tanısını sunmayı amaçladık. Bu olgu JAS'de AAA ve TA gelişen ilk olgudur.

Anahtar Sözcükler: Juvenil ankilozan spondilit, Ailesel Akdeniz Ateşi, Takayasu arteriti, pediatrik

Introduction

Juvenile ankylosing spondylitis (JAS) is defined as ankylosing spondylitis (AS) with symptom onset before the age of 16 years (1). Clinical presentation of JAS includes articular and extra-articular manifestations. Sacroiliitis is the most important characteristic articular manifestation (2). Familial Mediterranean Fever (FMF) is characterized by recurrent, self-limited flares of fever associated with polyserositis (3). Takayasu's arteritis (TA) presents with nonspecific symptoms, such as fatigue, weight loss, and low-grade fever in the early stage. As the disease progresses, it can manifest as vascular bruits, claudication, retinopathy and ischemia due to arterial occlusion (4).

Here in, we report a 17-year old female patient who presented with JAS and subsequently diagnosed with FMF and TA. In the literature, JAS coexisting with FMF and TA has not been reported yet.

Case

A 17-year-old female patient presented with the complaints of fever, abdominal pain and swelling in both feet. She was diagnosed with JAS two years ago with the complaints of inflammatory back pain, magnetic resonance imaging of the sacroiliac joint showing active sacroiliitis and human leukocyte antigen-B27 (HLA-B27) positivity. She described recurrent (periodic) fever, abdominal pain since she was 16 years old. She experienced intermittent attacks of abdominal pain and fever (39-40°C) for three to five days, then the symptoms resolved spontaneously and completely. She had a normal daily life during the symptom-free period. She was admitted to our rheumatology clinic for these reasons. Written informed consent was obtained from the patient. The general condition was moderate; she was well oriented and cooperative. Physical examination revealed feeble brachial and radial pulses on the right

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and left sides. Also, femoral-popliteal-and dorsalis pedis pulses were normal bilaterally. Heart rate was 98 beats-min and temperature was 38.5°C. Her blood pressure was 160/80 mmHg on the right upper limb and 110/70 on the left upper limb. The blood pressure on the right and left lower limbs was 160/74 and 163/72 mmHg, respectively. Murmur was absent over the abdominal aorta and epigastric region. No symptoms of vascular insufficiency were observed. Respiratory system examination revealed that both hemithoraces equally contributed to breathing and lung crackles were present in the left lower lobe. Physical examination of the locomotor system revealed tenderness and pain in both feets. Her ophthalmologic examination was normal. The patient's laboratory findings are presented in Table 1 Blood tests revealed anemia with a hemoglobin level of 8.2 g/dL, hematocrit of 30.4%, white cell count of 9.32 µL and platelet count of 517.000 µL. Also, laboratory data showed normal serum potassium and creatinine levels as well as glomerular filtration rate. Urine analysis was also normal. FMF mutation analysis showed *M694V* heterozigot mutation. According to the Tel-Hashomer criteria, the diagnosis of FMF was established (5). She met two major criteria (recurrent fever and serositis) and one minor criterion (positive response to colchicine treatment). Her electrocardiogram, transthoracic echocardiogram, magnetic resonance angiography (MRA) of the mesenteric arteries, thoracic, abdominal aorta and duplex ultrasonography were normal. MRA of the upper extremity showed left internal carotid artery stenosis and hypoplasia of the left vertebral artery. Furthermore, there was no flow in the left subclavian artery (Figure 1). To confirm the diagnosis of vasculitis a biopsy was taken from the left subclavian artery. Hypertrophy and mononuclear cell infiltration was seen in all the three layers in histological examination. Finally, angioplasty was performed. After surgery, her blood pressure was 110/70 mmHg on both the right and left upper limbs, 100/70 on both the right and left lower limbs. The patient was diagnosed as having FMF and TA simultaneously. Colchicine (1.5 mg), prednisolone (1 mg/kg body weight) and amlodipine (10 mg) were administered first. The patient had used acetylsalicylic acid (100 mg) and dipyridamole (150 mg) before and acetylsalicylic acid (100 mg) and clopidogrel (75 mg) after biopsy. Then, methotrexate (20 mg) and folic acid (5 mg) were started. Due to side effects, methotrexate was switched to azathioprine (150 mg) treatment. Her fever and abdominal pain regressed with colchicine treatment. She is currently under clinical follow-up.

Table 1. The laboratory values of the patient

Parameters	Result	Normal range
Hemoglobin	8.2 gr/dL	11.7-15.5 gr/dL
Hematocrit	30.4%	37-44
MCV	65.0 fL	80.4-95.9 fL
RDW	22.6	11.7-14.6
Leukocyte count	9.320 mkrL	3.800-11.000 mkrL
Platelet	517.000 mkrL	150.000-350.000 mkrL
Erythrocyte sedimentation rate	31 mm/h	0-20 mm/h
C-reactive protein	10.09 mg/L	0-6 mg/L
Urea	22 gr/dL	13-43 gr/dL
Creatinine	0.6 mg/dL	0.7-1.3 mg/dL
ALT	<6 IU/L	0-55 IU/L
Total protein	7.1 g/dL	6.4-8.3 g/dL
RF	1.95 IU/mL	0-18 IU/mL
C3	118.2 mg/dL	85-200 mg/dL
C4	38 mg/dL	20-50 mg/dL
c-ANCA/ p-ANCA	Negative	Negative
HLA-B27	positive	-
FMF mutation analysis	*M694V* heterozigot	-

MCV: Mean corpuscular volume, RDW: Red cell distribution width, ALT: Alanin aminotransferase, RF: Rheumatoid factor, ANCA: Anti-neutrophil cytoplasmic antibodie, HLA-B27: Human leukocyte antigen-B27, FMF: Familial Mediterranean Fever

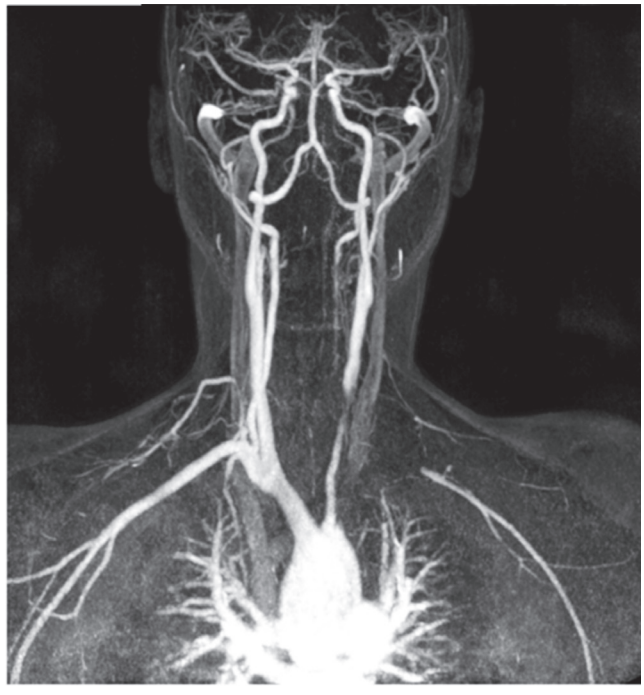

Figure 1. Upper extremity magnetic resonance angiography

Discussion

To our knowledge, this is the first reported case of JAS presenting with FMF and TA. In the literature, there have

been studies investigating the co-existeance of FMF and AS and prevalence of AS or spondyloarthritis (SpA) among FMF patients. Dilsen (6) reported the first case of FMF in a patient with AS in 1963. After this report, Kasifoglu et al. (7) reported that the frequency of sacroiliitis was 7% among 256 FMF patients. Akar et al. (8) reported fifteen FMF patients (7.5%) and nine unaffected first-degree relatives fulfilled the modified New York criteria for AS among 157 FMF patients (78.1%) and 233 (73%) unaffected first-degree relatives. Akkoc and Gul (9) reported increased prevalence of AS or SpA among FMF patients. How FMF develops in patients with AS is poorly understood. Kasifoglu et al. (7) suggested that HLA-B27 positivity and/or *M694V* mutation may play a role in the development of sacroiliitis and the severity of seronegative SpA. Also, Akar et al. (8) indicated that factors other than HLA-B27 play a role in the association of FMF and SpA/AS. *MEFV* gene variations may be one of the geographic/region-specific potential pathogenetic links between these two disorders in the Turkish population. Akkoc and Gul (9) stated that *MEFV* gene mutations regulates interleukin-1β (IL) activation. A genome-wide association study by Reveille et al. (10) included 2.053 unrelated AS cases among people of European descent and 5.140 ethnically matched controls, with replication in an independent cohort of 898 AS cases and 1.518 controls. It has been reported that four genetic loci associated with the risk of AS and identified a major role for the IL-23 and IL-1 cytokine pathways in AS. Therefore, association of FMF with AS can be explained. In their study in 2012, Zihni et al. (11) reported a case of co-existeance of FMF with TA.

FMF-associated vasculitis mechanisms involve environmental factors on the context of genetic predisposition. FMF-associated vasculitis cases had *MEFV* gene mutations. These mutations may be considered in the pathogenesis.

FMF is a prototype of autoinflammatory diseases. It is caused by inherited loss-of- function mutations in Pyrin which plays an important role in control and regulation of inflammation with an enzyme, Caspase-1, and it's target cytokine, IL-1β (12). Once activated, Caspase-1 proteolytically cleaves proIL-1β into an active IL-1β with a proinflammatory effect (13). Therefore, the mechanism of the overproduction of IL-1 in FMF can be explained.

Co-existeance of AS with TA is infrequent, and their association is even rarer. In a study conducted by Gan et al. (14), 6 patients fulfilled diagnostic criteria for AS and TA. The Authors indicated that there was no association between HLA-B27 and the pathogenesis of AS with TA.

Our patient is the first reported case of JAS presenting with FMF and TA. We suggest that FMF and TA can be seen in JAS patients. TA patients should be carefully followed until a final diagnosis can be clearly made.

Ethics

Informed Consent: A consent form was completed by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.G., B.S. Concept: B.S. Design: G.G., B.S. Data Collection or Processing: G.G., B.S. Analysis or Interpretation: G.G., B.S. Literature Search: G.G., B.S. Writing: B.S

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