

# A case of Takayasu's arteritis associated with familial Mediterranean fever

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Association of neutrophilic vasculitides such as Henoch-Schönlein purpura (HSP) and polyarteritis nodosa (PAN) with Familial Mediterranean fever (FMF), an autoinflammatory disorder, is well known (1, 2). However, to our knowledge, there has only been one patient reported with a coexistence of large-vessel vasculitides, namely Takayasu's arteritis (TA), with FMF (3). We, here, present a second patient with FMF and TA.

A 24-year-old male was referred due to bilateral pulselessness on his both ulnar and radial arteries, detected in his medical examination. He had been on colchicine therapy (1.5 mg/daily) for 7 years with a history of recurrent chest pain and fever attacks and was fulfilling the "Tel-Hashomer" criteria for FMF. He rarely had mild attacks after colchicine therapy without amyloidosis. In MEFV genetic analysis, he was heterozygote for R314R, E474E, Q476Q and p.D510D mutations. There was no history of FMF in his family, but he originated from Tokat, a city in Middle Anatolia with a very high incidence of FMF.

On physical examination, no pulses were detected bilaterally on his ulnar and radial arteries, without also a blood pressure detection on his right arm. The auscultation revealed bruits on both carotid and subclavian arteries. He had an elevated erythrocyte sedimentation rate (ESR) of 90 mm/hour and C-reactive protein (CRP) 6.1 mg/dl. With conventional digital subtraction angiography, high grade stenosis in cervical segment of left carotis common artery (CCA) (60%), left subclavian artery (60%) and wall irregularities in right CCA, right vertebral and right subclavian arteries with total occlusion in right axillary artery were detected. With the diagnosis of

TA, methylprednisolone (MP) 0.5 mg/kg daily and azathioprine 150 mg daily were prescribed. After a 9 month follow-up, the patient still had mild constitutional symptoms without new vascular ischaemic signs or bruits. CRP was 4.44 mg/dl, ESR was 70 mm/hour and MP could not be tapered to <10 mg/day. Azathioprine was stopped and cyclophosphamide (CyP) 750 mg/month was added to the therapy. Six months after the initiation of CyP, acute phase response began to decline. He was in clinical remission in his last visit, taking MP 6 mg/day and azathioprine 150 mg/day with an ESR: 11 mm/hour and CRP: 1.52 mg/dl.

Although TA is observed predominately in women (male/female: 1/8-10) (4), the presence of both our case and the previous one in male gender is remarkable. Our case also seems to have a refractory nature with a hard to suppress inflammatory response, which required us to use CyP. In this respect, the other reported TA case with FMF also required a more aggressive approach with a TNF- $\alpha$ -antagonist (3).

Most of the FMF-associated vasculitis cases had MEFV gene mutations, suggesting their role in vasculitis development. MEFV gene mutations upregulate innate immunity with increased IL-1 $\beta$  production, which serve as an exaggerated initial response to the endogenous or environmental factors (5). The majority of MEFV carriers have subclinical inflammation and the presence of these mutations are suggested to affect their disease course when they develop other rheumatological disorders (6).

Pathogenesis of TA mostly involves cell-mediated immunity. However, innate immune activation, IL-1 $\beta$  particularly, might perpetuate adaptive responses and have an effect on the course and prognosis of TA. Activation of Th17 T-cell subset, which might have a role in the early recruitment of neutrophils is recently demonstrated in TA (7). IL-1Ra-deficient (a natural antagonist of IL-1 $\beta$ ) mice also have transmural inflammation of elastic arteries with CD4+, IFN- $\gamma$

+ Th1 type infiltrates and suggested to be a model of human large-vessel vasculitides. In conclusion, we report a second TA patient associated with FMF in the literature. Although a clear association between the two disorders can not be proven, we suggest that increased IL-1 $\beta$  secretion in FMF patients might increase the susceptibility to or alter the disease course in TA patients.

F. ALIBAZ-ONER<sup>1</sup>, MD

N. YILMAZ<sup>2</sup>, MD

M. CAN<sup>1</sup>, MD

H. DIRESKENELI<sup>1</sup>, MD

<sup>1</sup>Department of Rheumatology, Marmara University, School of Medicine, Istanbul;

<sup>2</sup>Diyarbakir Government Hospital, Diyarbakir, Turkey.

Address correspondence to:

Fatma Alibaz-Oner, Fevzi Çakmak Mahallesi 1121, sokak no.14, 34200 Esenler-Istanbul, Turkey.

E-mail: falibaz@gmail.com

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