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Spondyloarthritis associated with familial Mediterranean fever: successful treatment with anakinra

Rheumatology key message

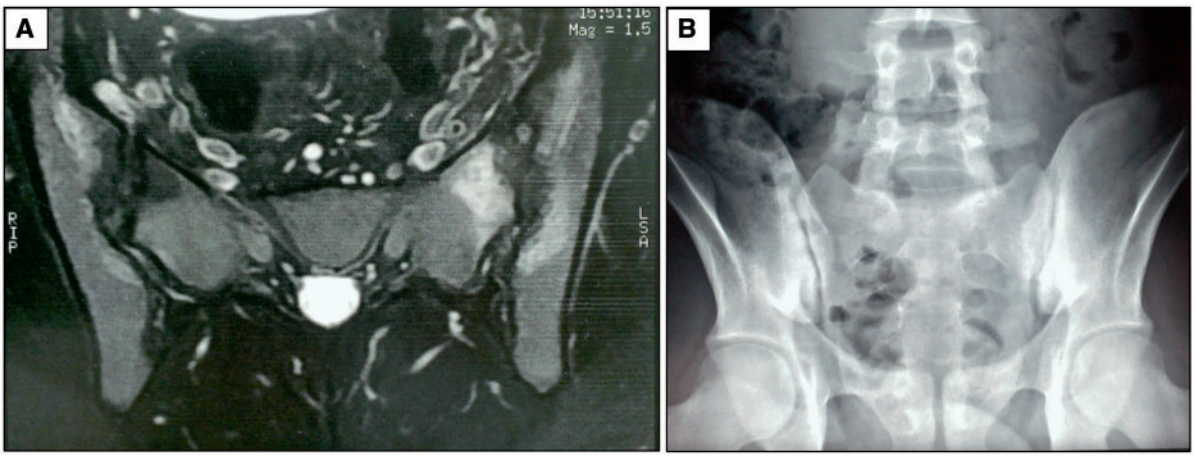
- Anakinra could be an effective treatment for colchicine-resistant patients with both spondyloarthritis and FMF.

Sir, FMF is an autosomal recessive, autoinflammatory disorder, with mutations in the *MEFV* gene. The clinical presentation is characterized by recurrent episodes of fever associated with abdominal, chest, joint and muscular pain [1, 2]. Colchicine is a safe daily treatment that can prevent both the recurrence of FMF attacks and the occurrence of inflammatory amyloidosis, but is usually ineffective in spondyloarthritis (SA) [2]. Patients with FMF and arthralgia can fulfil SA criteria, including sacroiliitis, enthesitis, inflammatory back pain mostly without spinal abnormalities at imaging and they are negative for HLA B27 [3, 4]. The recombinant IL-1 receptor antagonist anakinra has also been used in FMF patients unresponsive or intolerant to colchicine therapy [2, 5]. Anakinra has been tried for the treatment of isolated SA with modest efficacy in comparison with treatment with an anti-TNF inhibitor [6, 7]. We report here upon the efficacy of anakinra treatment in a patient displaying SA associated with FMF, and propose a literature review.

A 22-year-old North African man, presenting at our reference centre, had had typical FMF since childhood, with abdominal and thoracic pain accompanied by fever. Written informed consent was obtained from the patient. The diagnosis of FMF was genetically confirmed with the identification of a M694I homozygous mutation in *MEFV*. Daily colchicine treatment (1.5 mg/day) was successful in reducing/abolishing crises. For the past 2 years, he complained of daily inflammatory lower back pain and bilateral buttock pain, which occurred between FMF attacks. Lumbar movements were not limited (Schober's test 10 + 4 cm); chest expansion was +3 cm. Bilateral calcaneal enthesopathy in ankles was identified, and the BASDAI score was 5/10. The diagnoses of both FMF and SA in this patient were established on the basis of Tel-Hashomer criteria and ASAS criteria, respectively.

On admission, the laboratory findings revealed an elevated CRP concentration (18 mg/l, normal range <5 mg/l). He was negative for HLA B27 but had typical radiological findings of SA that were confirmed by bilateral sacroiliitis on MRI (Fig. 1). Axial SA was diagnosed, and he started therapy with a combination of NSAIDs and colchicine, increased to a dose of 2 mg/day. There was no improvement in lower back pain, buttock pain, frequency of FMF attacks and inflammatory syndrome during an 18-month treatment period. Injection of steroid into the sacroiliac

Fig. 1 Sacroilitis on MRI and standard radiography



(**A**) MRI showing left sacroillitis. (**B**) Standard radiography showing sacroilitiis.

joint had no effect. Despite colchicine treatment, FMF episodes persisted, with severe chest pain. SSZ (2 g/day) was added to the NSAID and colchicine treatment regimen for 6 months but did not reduce joint and lower back pain or the frequency of FMF episodes. He complained of daily pain, including pleural FMF pain with a BASDAI score 6/10. Twenty-one months after the initial diagnosis of SA, anakinra was started at 100 mg/day, showing dramatic efficacy in resolving pain and reducing recurrence of FMF episodes. The inflammatory syndrome regressed within 1 month. The patient's quality of life significantly improved; he gained weight and had neither axial SA nor FMF pain, sparing the use of antalgics and NSAIDs. The symptoms reappeared when he stopped anakinra injections for a few days. After 3 years of follow-up on anakinra treatment, the patient remained in complete remission. Lumbar movements and chest expansion were stable. The BASDAI score was 2/10. The colchicine dose was decreased to 1 mg daily.

In the literature, only a few cases of FMF have been reported in association with SA [3]; HLA B27 is mostly negative when studied, and often, the patients are found to be homozygous for the *MEFV* (M694V) variant. Four patients with SA and FMF displayed inflammatory amyloidosis, and six received colchicine alone with the usual efficacy. One patient received MTX in conjunction with a low prednisolone dose. Three patients received NSAID and one sulfasalazine. One article described a Jewish male patient with FMF and SA associated with myositis who received anakinra with good tolerance [8].

FMF can mimic SA. A diagnosis of FMF should be evoked in Mediterranean patients who display recurrent episodes of fever and HLA B27-negative, SA-like rheumatic pains. By contrast, when a patient with FMF displays symptoms such as sacroiliitis, criteria for SA and spinal abnormalities should be looked for, because these two conditions could be associated.

In conclusion, anakinra could constitute a therapeutic option for FMF patients with SA after unsuccessful treatment with colchicine associated with NSAID. Prospective studies should be conducted on a larger cohort of patients to confirm this result.

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Peroneal neuropathy in giant cell arteritis

Rheumatology key message

- A prior diagnosis of vasculitis does not preclude the development of non-vasculitic neuropathies.

SIR, Peripheral nerve involvement is frequent in systemic vasculitis, typically either mononeuritis multiplex or sensorimotor peripheral polyneuropathy. However, these are distinctly uncommon in GCA [1, 2] and should prompt consideration of alternative causes of neuropathy and reconsideration of the underlying diagnosis of GCA. We present three cases of peroneal neuropathy in patients with recently diagnosed GCA presenting to our institution over a 2 month period.

Patient 1 was a 57-year-old male who presented initially with bitemporal headache, recurrent amaurosis fugax, bilateral shoulder girdle pain and weight loss of 12 kg. Both temporal arteries (TAs) were tender. ESR was 26 mm/h and CRP was 16 mg/l. TA US demonstrated a positive halo sign. TA biopsy showed adventitial and intimal inflammatory infiltrates with no giant cells. He was diagnosed with GCA and had a complete response to 60 mg prednisolone. He re-presented 3 months later on a tapering dose of 20 mg prednisolone with acute left foot drop. He reported paraesthesia and a cold sensation on the dorsum of the foot. On examination, ankle dorsiflexion and eversion demonstrated reduced power of Medical Research Council (MRC) grade 3/5. He had no other symptoms and the remainder of the neurologic exam was normal. ESR was 6 mm/h and CRP was 1 mg/l, the remainder of his laboratory workup, including haemoglobin A1c, serum protein electrophoresis, ANCAs, ANA and viral serology, was normal. A nerve conduction study (NCS) confirmed a compressive left common peroneal neuropathy at the knee. He was managed conservatively with improvement in power to MRC grade 4+/5.

Patient 2 was a 64-year-old man who presented initially with right temporal headache, decreased right eye visual acuity, weight loss of 19 kg and night sweats. Both TAs were normal, fundoscopy revealed a pale swollen right optic disk consistent with anterior ischaemic optic neuropathy. ESR was 56 mm/h and CRP 156 was mg/l. TA US demonstrated bilateral halo sign, CT angiogram of the head, neck and thorax was normal and TA biopsy failed to sample the artery. He was diagnosed with GCA and had a complete response to i.v. methylprednisolone. One month later he re-presented on 60 mg prednisolone reporting a left foot drop and numbness on the dorsum of the foot, which he believed may have been present since disease onset. On examination, left ankle dorsiflexion and eversion demonstrated reduced power of MRC grade 3/5. He had no other symptoms. ESR at this stage was 7 mm/h and CRP was 2 mg/l. The remainder of his laboratory workup was normal, aside from an ANA of 1:400 with nucleolar pattern and a negative extractable nuclear antigen panel. MRI of the brain and lumbosacral spine was normal. An NCS confirmed a compressive common peroneal neuropathy at the knee. He was managed conservatively with improvement in power to MRC grade 4+/5.

Patient 3 was a 55-year-old man. He initially presented with bitemporal headache, recurrent left amaurosis fugax and bilateral shoulder girdle pain. The left TA was tender. ESR was 70 mm/h and CRP was 48 mg/l. TA US was normal. TA biopsy demonstrated an adventitial inflammatory infiltrate with no giant cells. He was diagnosed with GCA and commenced on prednisolone 60 mg with good response. He re-presented 2 months later on 20 mg prednisolone with sudden right foot drop and numbness on the dorsum of the foot. He reported onset after a prolonged period of sitting with crossed legs. On examination, right ankle dorsiflexion and eversion had reduced power of MRC grade 4/5. He had no other symptoms. ESR was 4 mm/h and CRP was 1 mg/l; the remainder of his laboratory workup was normal. His symptoms resolved over 2 weeks and an NCS performed after resolution was normal.

Our case series highlights the importance of the correct determination of the aetiology of any new symptoms in patients with pre-existing vasculitis. The three patients described here were ultimately diagnosed with compressive common peroneal neuropathies, two most likely due to rapid weight loss and the other due to prolonged leg crossing. A prior diagnosis of GCA does not preclude the development of non-vasculitic neuropathies, including compressive neuropathies. The occurrence of peripheral neuropathy due to direct vasculitic involvement from GCA is disputed, but if it exists, it is rare [1]. Mononeuritis