

Case report

Refractory polymyalgia rheumatica as presenting manifestation of large-vessel vasculitis associated to sarcoidosis. Successful response to adalimumab

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ABSTRACT

Sarcoidosis may present with musculoskeletal features or mimic rheumatic diseases. We report on a patient who had been initially diagnosed as having polymyalgia rheumatica. Because of refractory disease associated to atypical features such as severe inflammatory low back pain, dull and achy pain in the thighs, claudication of the lower limbs and bad response to corticosteroids and methotrexate (MTX), an 18F-fluorodeoxyglucosepositron emission tomography with CT (FDG PET/CT) was performed. This technique disclosed data suggestive of arteritis of large vessels involving the ascending, arch and descending aorta as well as high FDG uptake in the femoral and posterior tibial arteries of both lower extremities. Also, increased FDG uptake was observed in the right paratracheal, retrotracheal, subcarinal, gastrohepatic ligament, coeliac and right renal hilar lymph nodes. Four lymph nodes, taken during mediastinoscopy, confirmed a diagnosis of sarcoidosis. Treatment with adalimumab (40 mg every 2 weeks subcutaneously) along with prednisone and MTX was initiated yielding progressive improvement of symptoms and normalisation of laboratory abnormalities. Five months after the onset of adalimumab a new FDG PET/CT showed complete absence of uptake of lymph nodes as well as decrease of vascular FDG uptake. To our knowledge, this is the first patient treated with adalimumab because of a large-vessel vasculitis in the setting of sarcoidosis refractory to conventional therapy. This case reinforces the claim that sarcoidosis should be considered a diagnostic challenge in the assessment of patients presenting with inflammatory musculoskeletal symptoms.

Introduction

Sarcoidosis is a multisystem disease with predisposition to lung involvement. This heterogeneous granulomatous disease may coexist with or mimic rheumatic diseases such as systemic lupus erythematosus, rheumatoid arthritis, and ankylosing spondylitis (1). Musculoskeletal features may be observed in patients with sarcoidosis (1, 2). However, to the best of our knowledge, polymyalgia rheumatica (PMR) as presenting manifestation preceding a diagnosis of this condition has not been described. Also, although sarcoidosis may involve any part of the body, vascular involvement in the setting of this disease has been uncommonly reported (3, 4). Correctly diagnosing sarcoidosis may be a challenge. Therefore, rheumatologists should consider a diagnosis of this condition in patients presenting with musculoskeletal manifestations, in particular if atypical features are present.

Case report

We describe the case of a 56-year-old man who presented to the rheumatology outpatient clinic because of a flare of PMR.

His past medical history was unremarkable. Almost 2 years before he had been diagnosed as having isolated PMR, because of a 5-month-history of pain and aching involving the neck, the shoulder girdle and proximal aspects of arms, and the pelvic girdle and proximal aspects of legs, along with morning stiffness and elevation of acute phase reactants. Treatment with prednisone (15 mg/day) yielded a rapid improvement of symptoms in less than a week. Because of 2 flares of musculoskeletal symptoms that occurred when pred-

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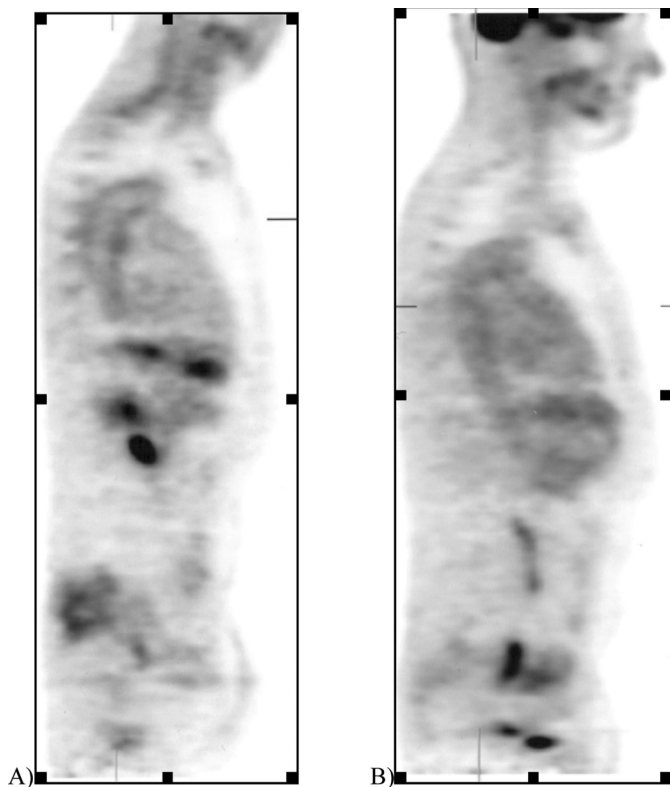


Fig. 1.
A. Moderate diffuse FDG uptake in the ascending, arch and descending aorta.
B. Decrease of vascular FDG uptake following anti-TNF-alpha therapy.

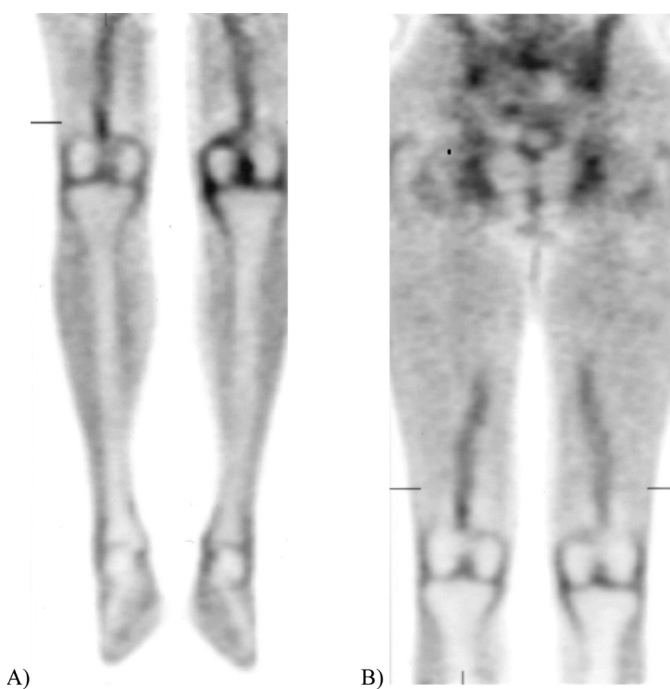


Fig. 2.
A. Markedly increased FDG uptake in the femoral and posterior tibial arteries of the lower limbs.
B. Decrease of vascular FDG uptake following anti-TNF-alpha therapy.

nisone dose was tapered below 10 mg/day a temporal artery biopsy that yielded negative results for giant cell arteritis was performed. Methotrexate (MTX) therapy (10 mg/week progressively increased up to 20 mg/week) was started. Prednisone dose was tapered to discontinuation 20 months after the initial diagnosis of PMR. However, following

corticosteroid withdrawal and despite MTX treatment the patient had a new flare of the PMR associated to fatigue, low-grade fever, arthralgias, severe inflammatory low back pain and dull and achy pain in the thighs along with claudication of the lower limbs. The patient denied ocular, cutaneous or respiratory manifestations. On physical examina-

tion no cardiac murmurs were heard, and chest and abdominal examination was also normal. No skin lesions were observed and an ophthalmic examination did not show the presence of uveitis or any other ocular finding. At that time laboratory parameters disclosed a mild inflammatory process with ESR 33 mm/1st hour and C-reactive protein 21.5 mg/L. Apart from a slight elevation of hepatic function tests, blood cell count and serum chemistry and urine analyses, including gamma-globulin and serum and urinary calcium levels, were normal. Antinuclear antibodies, rheumatoid factor, anti-CCP antibodies, serum complement C3 and C4 levels and angiotensin-converting enzyme were negative or normal. Likewise, serological tests for hepatitis B and C, HIV, cytomegalovirus, parvovirus B19, mononucleosis, borrelia, and brucella and skin tuberculin test were negative. Also, a chest x-ray was normal. Because of that, taking into account the atypical course for a PMR a FDG PET/CT was performed to exclude the presence of aortitis. FDG PET/CT disclosed an inflammatory process with moderate diffuse increased metabolism in the ascending, arch and descending aorta (grade 2 on a 0–3 scale) and markedly increased FDG uptake in the femoral and posterior tibial arteries on both sides (grade 3 on a 0–3 scale) consistent with vasculitis of large and medium vessels (Fig. 1A, 2A). Additionally, besides these data suggestive of arteritis of large and medium vessels involving mainly the aorta and lower extremities, increased FDG uptake was observed in the right supraclavicular, right paratracheal, retrotracheal, subcarinal, gastrohepatic ligament, coeliac and right renal hilar lymph nodes (Fig. 3A).

Respiratory function tests showed a slight decrease in CO pulmonary diffusion. Since results of bronchoscopic biopsies did not yield a diagnosis, a mediastinoscopy was performed. Interestingly, four lymph nodes, taken during mediastinoscopy, confirmed a diagnosis of sarcoidosis (Fig. 4A, 4B). Due to the presence of vasculitis associated with sarcoidosis that had been refractory to corticosteroid plus MTX

therapy, treatment with the anti-TNF-alpha monoclonal antibody-adalimumab (40 mg every 2 weeks subcutaneously) along with prednisone and MTX was initiated with progressive improvement of symptoms and normalisation of laboratory abnormalities. Five months after the onset of adalimumab therapy the patient was asymptomatic, prednisone had been successfully tapered to a dose below 10 mg/day, and a new FDG PET/CT showed complete absence of uptake of lymph nodes as well as decrease of vascular FDG uptake (grade 1 on a 0–3 scale) (Fig. 1B, 2B, 3B).

Discussion

This case reinforces the claim that sarcoidosis should be considered a diagnostic challenge in the assessment of patients presenting with inflammatory musculoskeletal symptoms.

There are a number of points in this case that deserve to be discussed. Firstly, the patient presented with PMR features. PMR is an inflammatory syndrome characterised by pain and aching involving the neck and the shoulder and pelvic girdles in individuals over the age of 50 years (5). It is generally a benign and self-limited condition. A diagnosis of PMR is relatively straightforward when typical symptoms are present. However, none of the clinical and laboratory findings in PMR are specific and several other diseases may present with similar musculoskeletal aching and the exclusion of these processes is important as their therapy and prognosis differ greatly from the classic therapy used in a “pure” PMR (6, 7). Like in our case, the presence of atypical features or inappropriate response to corticosteroids (prednisone 10 to 20 mg/day or equivalent doses) should be considered red flags for the presence of a condition mimicking PMR but different from isolated PMR.

Secondly, our patient had a vasculitis in the setting of sarcoidosis. As described in epidemiological studies, sarcoidosis is as an uncommon cause of secondary vasculitis (8). Moreover, although vasculitis associated to sarcoidosis in adults presents in half of the cases as a small-vessel leukocytoclastic vasculitis

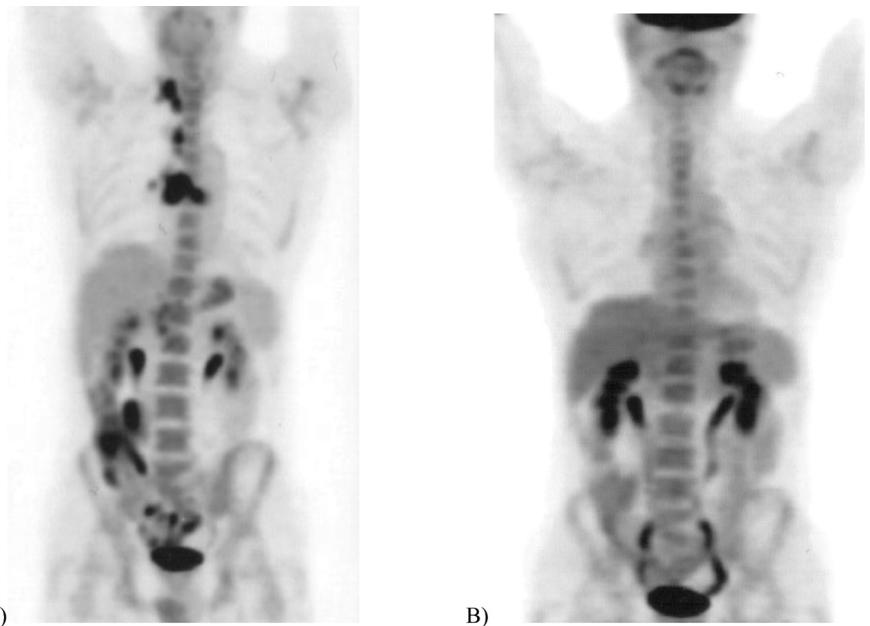
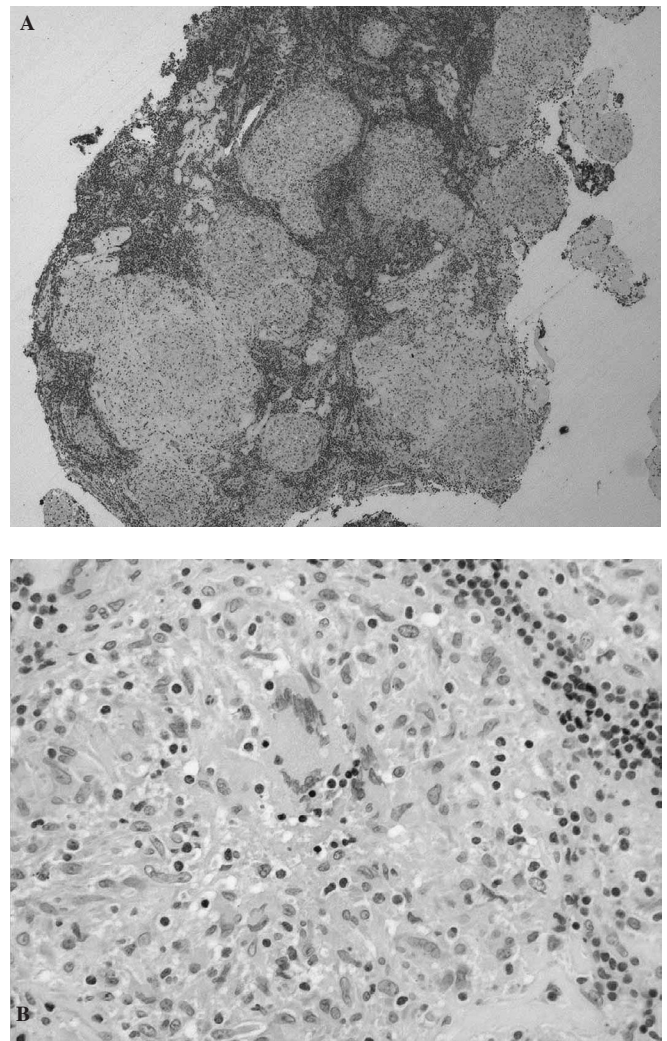


Fig. 3. A. Increased FDG uptake in the right supraclavicular, right paratracheal, retrotracheal, subcarinal, gastrohepatic ligament, coeliac and right renal hilar lymph nodes. B. Complete absence of uptake of lymph nodes following anti-TNF-alpha therapy.

Fig. 4. A. Non-caseating chronic granulomatous lymphadenitis, consistent with sarcoidosis. B. Presence of sarcoid granulomas with epithelioid cells, scarce lymphocytes and some multinucleated giant cells.



mimicking hypersensitivity vasculitis (3, 9), our patient had a large-vessel vasculitis. Cases of sarcoidosis associated to polyarteritis nodosa, microscopic polyangiitis, Wegener's granulomatosis or Takayasu's arteritis (TA) have also been reported (3, 4, 10). In this regard, Weiler *et al.* described a case of concurrence of sarcoidosis and aortitis that fulfilled definitions for TA. However, unlike our case, there was a long delay between the onset of clinical features of sarcoidosis and the diagnosis of TA (4). Also, in their report, Weiler *et al.* conducted a literature review and described another 4 patients diagnosed with sarcoidosis that fulfilled definitions for TA and another for aortitis presumably due to sarcoidosis (4). Likewise, 3 out of the 6 cases with sarcoidosis and vasculitis reported by Fernandes *et al.* showed features of large-vessel vasculitis (3).

Thirdly, as emphasised by Pipitone and Salvarani, FDG PET/CT may be useful to detect large-vessel vasculitis (11). Interestingly, by this technique these authors disclosed a vasculitis in a patient presenting with PMR features (12). However, in contrast to our report, the vasculitis involved only the lower extremities (12).

Finally, an additional point that deserves to be discussed was the therapy used in the management of our patient with sarcoidosis. In this regard, MTX is generally the preferred agent for treat-

ment of chronic sarcoidosis when corticosteroids have inadequate efficacy and/or severe adverse effects (13). Regrettably, in our case neither corticosteroids alone nor combination of corticosteroids and MTX did have a good result in terms of improvement of the disease. Interestingly, although different severe complications of sarcoidosis such as posterior uveitis, neurosarcoidosis and lupus pernio have been successfully treated with anti-TNF-alpha monoclonal antibodies (14), to our knowledge, in this report we describe the first case ever treated with adalimumab because of a large-vessel vasculitis in the setting of sarcoidosis refractory to conventional therapy. Therefore, the beneficial effect experienced by our patient following this biologic therapy supports the use of anti-TNF-alpha monoclonal antibodies in the management of patients with severe refractory sarcoidosis.

In conclusion, the present study highlights the importance of considering a diagnosis of sarcoidosis in patient presenting with musculoskeletal features.

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