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Radiographical bony lesions after discontinuation of immunosuppressant therapy: bone involvement in sarcoidosis

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SUMMARY

We describe a patient who had failed renal transplant after 13 years, eventually requiring a graft nephrectomy and discontinuation of immunosuppressive therapy, including antithymocyte globulin, tacrolimus and mycophenolate while on steroid avoidance protocol. Within a few months of complete discontinuation of the immunosuppressive medications, she developed lower back pain associated with numbness in her right anterolateral thigh. The radiological imaging demonstrated multiple bony lesions throughout her axial and appendicular skeleton with normal pulmonary findings. A computerised tomography-guided bone biopsy from the left iliac crest revealed fragments of bone with granulomatous inflammation, thus making the diagnosis of extrapulmonary sarcoidosis. Initiating treatment with prednisone resulted in near-complete resolution of symptoms. Long-term immunosuppressive therapy is administered to all renal transplant recipients to help prevent acute rejection and loss of renal allograft. This case highlights that immunosuppressants can conceal the presence of underlying conditions in transplant patients.

BACKGROUND

Sarcoidosis is a granulomatous disorder of unknown cause that affects multiple organs.[1] Bone involvement has been reported in 1%–13% of patients with sarcoidosis.[1–5] Our case highlights the importance of having a broad differential diagnosis while using appropriate imaging modalities and subsequently biopsy for making the diagnosis. Positron emission tomography/CT (PET-CT) and conventional MRI are sensitive in detecting sarcoidosis bone lesions but are not always reliable in differentiating sarcoidosis bone lesions from metastatic disease, thus often requiring bone biopsy.[2 3] This incidence of bone involvement is probably underestimated in certain patient series because bone involvement is often asymptomatic[4]; however, in this case, symptoms occurred insidiously once immunosuppressants were stopped.

CASE PRESENTATION

A female of African descent in her 50s, with a history of end-stage renal disease, presented to the family medicine outpatient clinic with insidious gradually progressive low back pain, radiating to the posterior aspect of her legs and her toes associated with numbness in her right anterolateral thigh. The back pain and leg pain were aggravated with sitting, standing and walking with associated paresthesias but without lower extremity muscle weakness.

The patient had a remote history of secondary focal segmental glomerular sclerosis diagnosed via biopsy in the setting of solitary congenital kidney and ultimately requiring peritoneal dialysis in which she eventually had living unrelated renal transplant after a year of requiring peritoneal dialysis. 13 years prior to the case presentation at hand, she underwent a living-unrelated renal transplant for ESRD (End-stage renal disease) with excellent allograft function with steroid-sparing induction therapy with antithymocyte globulin dose at 1.5 mg/kg per day for 7 days followed by chronic immunosuppressive treatment with tacrolimus and mycophenolate. Previous infections including coccidioidomycosis that occurred years prior to transplantation had been resolved without treatment or sequelae. Unfortunately, 13 years after transplantation, the patient presented with hypertensive urgency and acute kidney injury ultimately leading to renal failure. A renal biopsy revealed T-cell-mediated transplant rejection. She was treated with haemodialysis and underwent allograft nephrectomy 3 months later which led to the discontinuation of immunosuppressants of tacrolimus and mycophenolate.

Body aches and back pain started insidiously over the ensuing 6 months after having allograft nephrectomy and discontinuing the immunosuppressants. There were no associated fevers, chills, night sweats, unintentional weight loss, or other systemic signs of infection. Clinical evaluation by her primary care physician included laboratory investigations of a complete blood count revealing normocytic anaemia of 9.4 g/dL, hematocrit of 31.7% and normal platelets, leucocyte count and differential, an abnormal creatinine consistent with her baseline of 8 g/dL, normal electrolytes, urine analysis revealing proteinuria and a normal sed rate of 25 mm per hour and negative blood and urine cultures. MRI of the lumbar spine revealed multiple bony lesions throughout the lumbar spine, sacrum and bilateral iliac wings suspicious of metastatic neoplasm (figure 1). CT scan of the chest revealed completely normal pulmonary parenchyma without nodules, peribronchovascular infiltrates and mediastinal

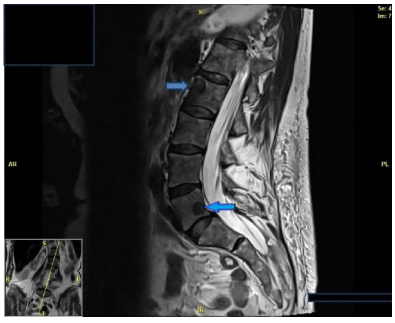

Figure 1 MRI denoting lesions of the lumbar spine.

or hilar lymphadenopathy. Fluorodeoxyglucose PET-CT (FDG-PET-CT) was then performed which revealed multifocal intensely hypermetabolic bone lesions throughout the axial and proximal appendicular skeleton (figure 2). Further laboratory investigations included normal coccidioidomycosis, *Blastomyces* and *Cryptococcus* serology. A CT-guided biopsy of bone marrow taken from the left iliac crest revealed fragments of bone with non-caseating granulomatous inflammation and scarring without any evidence of malignancy. Grocott's methenamine silver and acid-fast bacillus stains were negative. Tissue cultures for fungi, bacteria and acid-fast bacilli were also negative ruling out an infectious cause of these lesions.[5] As such, the diagnosis of skeletal sarcoidosis was made.[6]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included metastatic bone lesion, multiple myeloma, brown tumours of hypothyroidism, lymphoma, osteomyelitis, Paget's disease of bone and fibrous dysplasia. CT-guided biopsy ruled out malignancy and infection.

TREATMENT

Prednisone treatment with 40 mg per day was initiated for 6 weeks and gradually tapered down. Three months after starting the treatment, 18-FDG PET/CT scan showed complete resolution of all tracer-avid osseous uptake (figure 3). The patient was maintained on 10 mg prednisone per day. The patient noted subsequent improvement and was able to return to her usual activities of daily living.

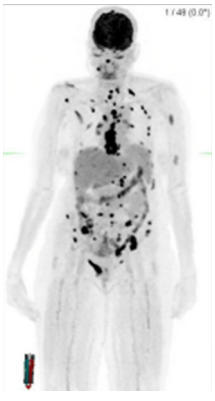

Figure 2 PET scan, non-lytic multifocal intensely hypermetabolic bone lesions throughout the axial and proximal appendicular skeleton.

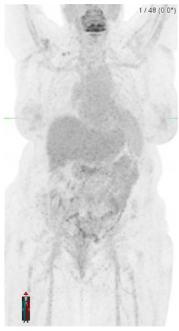

Figure 3 PET scan after initiation of prednisone, 3 months later. Complete resolution of all tracer-avid osseous uptake.

OUTCOME AND FOLLOW-UP

The patient noted subsequent improvement in pain and was able to return to her usual activities of daily living.

The patient was eventually relisted as candidate for renal transplant.

Routine serial imaging continued to note resolution of the skeletal lesions.

Two years after the incidence of this case report, the patient received a renal transplant.

While under immunosuppression, there has not been a recurrence of skeletal sarcoidosis.

DISCUSSION

Sarcoidosis, a granulomatous disorder, predominantly affects the organ systems like the lungs, skin, lymph nodes, eyes and liver with an unusual involvement of the skeletal system. The bone involvement in sarcoid is uncommon and is often associated with cutaneous, lymphatic or visceral involvement representing the chronic state of the disease.[6] Osseous sarcoidosis has been reported to involve the bones of the hands and feet. Axial skeleton involvement is rarely reported.[7] Apart from the higher disease incidence in individuals of African descent, such individuals are also diagnosed at a slightly earlier age and have a higher frequency of extrapulmonary and symptomatic disease. Middle-aged women of African descent (30–39 years) have a 20% higher risk of sarcoidosis compared with men of the same age and ethnicity, who have the next highest sarcoidosis risk.[8] The presence of non-caseating granulomas is the histopathologic hallmark of the disease, and clinical picture depends on the organs affected. Comorbid conditions are common in sarcoidosis such as cardiovascular and pulmonary diseases. The clinical picture is variable and often depends on the organs affected, the most common presentations including bilateral hilar adenopathy, pulmonary reticular and/or nodular opacities, and skin, joint or eye lesions.

In our patient, sarcoidosis affected both axial and appendicular skeleton, without involving the lungs. Our patient's clinical complaints of low back pain with radiculopathy led to MRI of lumbar spine which showed multiple bony lesions, and ultimately, FDG-PET-CT revealed non-lytic multifocal intensely hypermetabolic bone lesions throughout the axial and proximal appendicular skeleton. PET-CT appears to be more accurate and contributes to a better evaluation of extrapulmonary sarcoidosis.[5] The most noted pattern of the sarcoid bone lesions is lytic, sclerotic or mixed particularly in the axial skeleton and long bones.[9] The differential diagnosis of multiple osteolytic lesions is

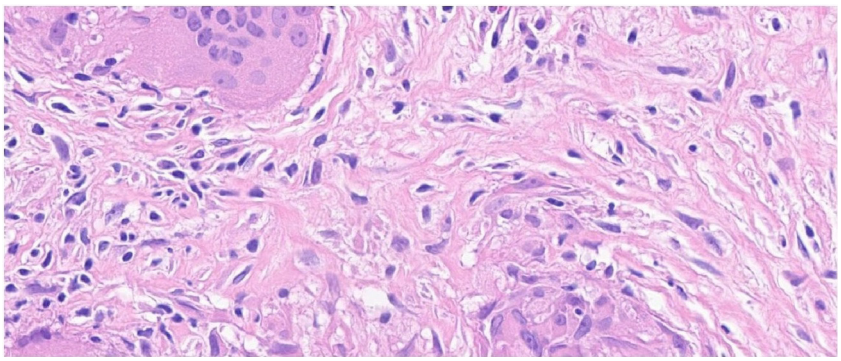

Figure 4 Histopathologic section: negative for malignancy.

extensive which includes metastases secondary to the malignancy, multiple myeloma, brown tumours of hyperparathyroidism, lymphoma, histiocytosis, osteomyelitis, Paget's disease and fibrous dysplasia.[5] Our patient's clinical presentation, imaging findings and ultimately biopsy results ruled out these considerations. An extrathoracic biopsy demonstrating non-necrotising granulomas with negative stains and cultures for pathogens allowed for a confident diagnosis of sarcoid in this case (figure 4).

By prevalence, the sarcoid bone lesions are expected to be encountered less frequently on routine MRI than the metastatic bony lesions. Skeletal metastasis is the most common malignancy of the bone in adults and is the third most common site of metastatic involvement after the lungs and liver.[9] These findings on the radiological imaging alone cannot differentiate malignancy from sarcoidosis. A CT-guided biopsy from the lesion site was performed which revealed fragments of bone with granulomatous inflammation and scarring, ruling out malignancy.[7] Microbiological studies including stains of biopsy samples did not reveal an infectious cause for granulomatous disease such as tuberculosis, coccidiomycosis or additional deep-seated fungal infections.

The granulomas are considered as the non-renal source of 1,25-dihydroxy-vitamin D3, which is increased in these patients leading to an increase in intestinal absorption of calcium causing hypercalcaemia.[10] In our patient, there was an abnormal increase in the concentrations of 1,25-dihydroxy-vitamin D3; however, her calcium was in normal range (Ca+2 = 10.1). Her other laboratory investigations such as ACE were at a normal level. An ACE level may be increased in sarcoidosis but is neither sensitive nor specific for the condition and should not be considered a routine diagnostic test. Overall serum ACE levels have a poor predictive value in sarcoidosis.[10 11]

Glucocorticoids are considered the first line of therapy for sarcoidosis which helps in reducing the pain and the soft tissue inflammation.[12 13] We started our patient on a single dose of 40 mg prednisone daily for a period of 6 weeks and then gradually reduced the dose to a maintenance level of 10 mg to prevent relapses. Once started back on immunosuppressive medications post her second transplant, the administration of systemic steroids was no longer necessary in this case. Symptomatic relief may also be obtained by other medications like colchicine, indomethacin and other non-steroidal anti-inflammatory agents, but these were not given to our patient due to her end-stage renal disease. Alternative treatments like methotrexate are considered in patients who fail to respond to corticosteroids or in those who require additional treatment to potentiate prednisone doses <20 mg.[14]

Learning points

- It is important that clinicians have a broad differential diagnosis including sarcoidosis when evaluating skeletal lesions.
- Immunosuppressant therapy can potentially conceal sarcoid, particularly in individuals who are at risk such as in individuals of African descent.
- Radiological imaging alone cannot differentiate malignancy from sarcoid; thus, biopsy is warranted.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

REFERENCES

1 Baughman RP, Lower EE, du Bois RM. Sarcoidosis. *The Lancet* 2003;361:1111–8.
2 Conte G, Zugni F, Colleoni M, *et al*. Sarcoidosis with bone involvement mimicking metastatic disease at 18F-FDG PET/CT: problem solving by diffusion whole-body MRI. *Ecancermedicalscience* 2015;9:537.
3 Bargagli E, Olivieri C, Penza F, *et al*. Rare Localizations of bone Sarcoidosis: two case reports and review of the literature. *Rheumatol Int* 2011;31:1503–6.
4 Zhou Y, Lower EE, Li H, *et al*. Clinical characteristics of patients with bone sarcoidosis. *Seminars in Arthritis and Rheumatism* 2017;47:143–8.
5 Talmi D, Smith S, Mulligan ME. Central Skeletal Sarcoidosis mimicking metastatic disease. *Skeletal Radiol* 2008;37:757–61.
6 Mehrotra P, Muller M, Higgins B, *et al*. An unusual cause of widespread Lytic bone lesions caused by Sarcoidosis. *J Radiol Case Rep* 2011;5:1:1–7:.
7 Ben Hassine I, Rein C, Comarmond C, *et al*. Osseous Sarcoidosis: a multicenter retrospective case-control study of 48 patients. *Joint Bone Spine* 2019;86:789–93.

8 Rybicki BA, Major M, Popovich J, *et al*. Racial differences in Sarcoidosis incidence: a 5-year study in a health maintenance organization. *American Journal of Epidemiology* 1997;145:234–41.
9 Moore SL, Kransdorf MJ, Schweitzer ME, *et al*. Can Sarcoidosis and metastatic bone lesions be reliably differentiated on routine MRI *AJR Am J Roentgenol* 2012;198:1387–93.
10 Lieberman J. Elevation of serum Angiotension-converting-enzyme (ACE) level in Sarcoidosis. *Am J Med* 1975;59:365–72.
11 Ziegenhagen MW, Rothe ME, Schlaak M, *et al*. Bronchoalveolar and serological parameters reflecting the severity of Sarcoidosis. *Eur Respir J* 2003;21:407–13.
12 Jacob A. Disseminated Skeletal Sarcoidosis mimicking malignant metastasis. In: *D32. ILD: CASE REPORTS II. American Thoracic Society*. 2018.
13 Kuzyshyn H, Feinstein D, Kolasinski SL, *et al*. Osseous Sarcoidosis: a case series. *Rheumatol Int* 2015;35:925–33.
14 Wilcox A, Bharadwaj P, Sharma OP. Bone Sarcoidosis. *Curr Opin Rheumatol* 2000;12:321–30.