A dual diagnosis of skeletal tuberculosis and sarcoidosis: case report

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Abstract

Tuberculosis (TB) is a common granulomatous infection in South Africa. The prevalence of TB and the extent of multi-system involvement have escalated since the advent of the HIV pandemic in the 1980's. The combination of TB and sarcoidosis is an uncommon concomitant diagnosis but has been described in the literature in multiple different contexts. We report the first known case of multisystem tuberculosis and sarcoidosis with multifocal skeletal lesions in a patient with complicated diabetes mellitus. We anticipate increasing the index of suspicion among clinicians of such a potential combination, especially in a population with impaired immunity such as in individuals with poorly controlled diabetes mellitus.

Key words: Sarcoidosis, Tuberculosis, Tubercular-sarcoidosis

Introduction

The clinical, histological and radiological differentiation of sarcoidosis from tuberculosis (TB) can be challenging owing to their multiple similarities. However, it is very important to differentiate the two since the therapeutic strategies to treat either one of them are completely different. The concomitant diagnosis of both conditions in the same patient can be even more challenging. We describe a rare case presentation of concomitant TB and sarcoidosis affecting the skeletal system in multiple sites in an immunocompromised host.

Case report

We report a case of multisystem tuberculosis TB and sarcoidosis in an HIV negative 39-year-old female with a medical background of hypertension and type 1 diabetes mellitus complicated by early retinopathy and advanced diabetic nephropathy with chronic renal failure and severe proteinuria.

The initial presentation to Tygerberg Hospital was in January 2016 with delirium secondary to non-PTH mediated severe hypercalcemia. An erythematous skin lesion suspicious for sarcoidosis was noted on the left shin and non- caseating granulomatous pathology with a negative Ziehl Nelson staining (ZN) was confirmed on biopsy (Table 1). Radiological features of hilar adenopathy and bilateral apical reticulo-nodular lung infiltrates (Figure 1*)* with restricted lung functions supported the diagnosis of sarcoidosis. A negative sputum GeneXpert made the diagnosis of pulmonary tuberculosis unlikely and the TB sputum culture detected no growth after 40 days. A diagnosis of multisystem sarcoidosis with restricted lung functions complicated by severe hypercalcemia was made, and she was treated with a combination of corticosteroids and bisphosphonate therapy.

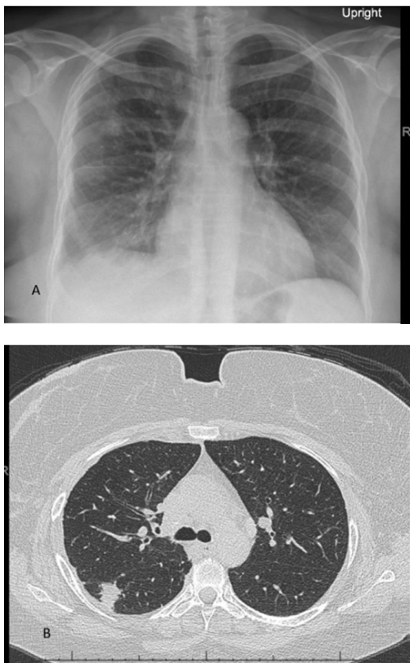
Table 1: Blood, urine, microbiology and histology results

Biochemical tests	2016		2017		2019		Range
Calcium							
• Serum (mmol/L)	3.82	3.69	2.60	2.44	2.48	2.54	2.15-2.50
• Urine (mmol/24hrs)	0.51				<0.20		2.5-7.5
S- PTH (pmol/L)	2.0	2.7					1.5-7.6
S- Vit D (nmol/L)	<10.5	23.7	31.1	74.89			>72.5
S- ALP (U/L)	400	168	99	129	209	169	42-98
S- ACE (U/L)	2	78			1		8-52
HBA1C (%)	8.9	9.9	7.5	8.9	8.0	8.6	<5.6
S- Urea (mmol/L)	9.3	12.9	14.8	10.5	12.5	17.5	2.1-7.1
S- Creat (umol/L)	123	127	206	164	183	268	49-90
Urine PCR (g/24hrs)					4.00	2.84	<0.3

	Microbiological and histopathological tests		
	2016	2017	2019
Sputum	GXP negative.		GXP positive. RIF sensitive.
Skin biopsy	Left shin region: Non-caseating granulomas seen. ZN stain negative for TB. Culture negative for TB on Bactec MGIT medium after 40 days.		Abdominal wall region: Non- caseating granulomas seen. Culture negative for TB on Bactec MGIT medium after 40 days.
Psoas muscle aspirate			Positive culture for TB on Bactec MGIT medium after 14 days. RIF and INH resistant.

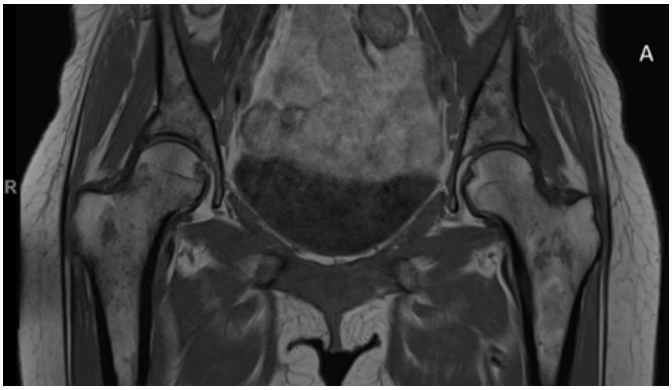
Abbreviations: S. (Serum); Ca (calcium); U. Ca (urine calcium); PTH (parathyroid hormone); Vit D (vitamin D); ALP (alkaline phosphatase) ; ACE (angiotensin converting enzyme); HBA1C (glycated hemoglobin); Creat (creatinine); UPCR (urine protein creatinine ratio); GXP (GeneXpert assay); ZN (Ziehl Neelsen); AFB (acid-fast bacilli); Bactec MGIT (Becton Dickinson and Company Mycobacterium Growth Indicator Tube); RIF (rifampicin); INH (isoniazid)

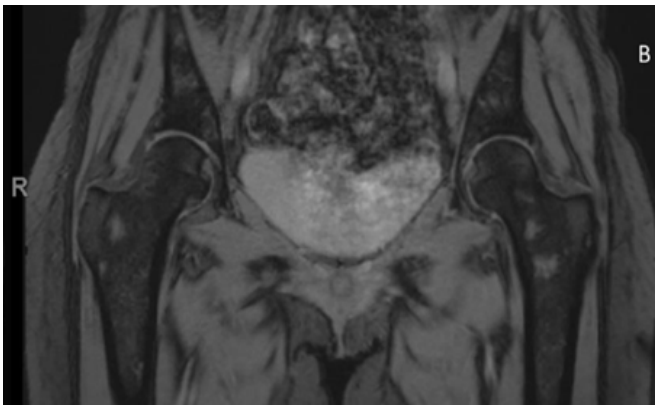
Figure 1: **A.** Plain chest radiograph demonstrating a reticulo-nodular infiltrative pattern. **B.** High resolution CT chest image demonstrating paraseptal and subpleural nodules compatible with stage II sarcoidosis



About two weeks into therapy, the patient developed severe left hip and buttock pain. No abnormalities were detected on plain radiograph films of the affected regions, but subsequent magnetic resonance imaging revealed extensive T2 hyper-intense and T1 hypo-intense focal lesions of the proximal femur, the pelvis and the sacrum. These lesions were suggestive of either skeletal or bone marrow sarcoid involvement (Figure 2). A bone marrow aspirate performed at the time showed morphological and immunohistochemical features suggestive of bone marrow infiltration by sarcoidosis. The ZN staining was negative. The immune-modulatory treatment was continued but modified after a few months to include the steroid sparing agent methotrexate due to severe cushingoid features and problematic glycemic control. Some regression of the observed skeletal lesions on MRI scan was confirmed 9 months later and the patient's symptoms also improved.

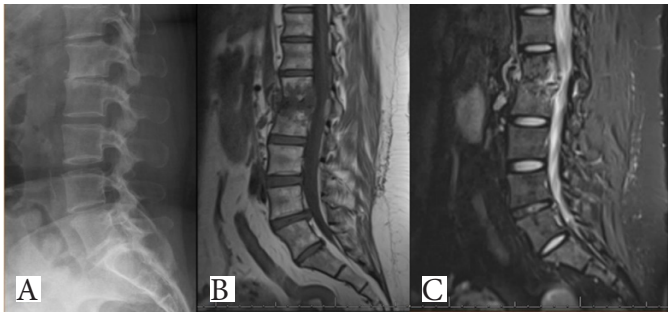
Figure 2: **A**. MRI T1 weighted image demonstrating multiple hypointense lesions of the pelvis and proximal femurs. **B.** MRI T2 weighted image demonstrating multiple hyperintense lesions of the pelvis and proximal femurs. Findings consistent with skeletal inflammatory lesions





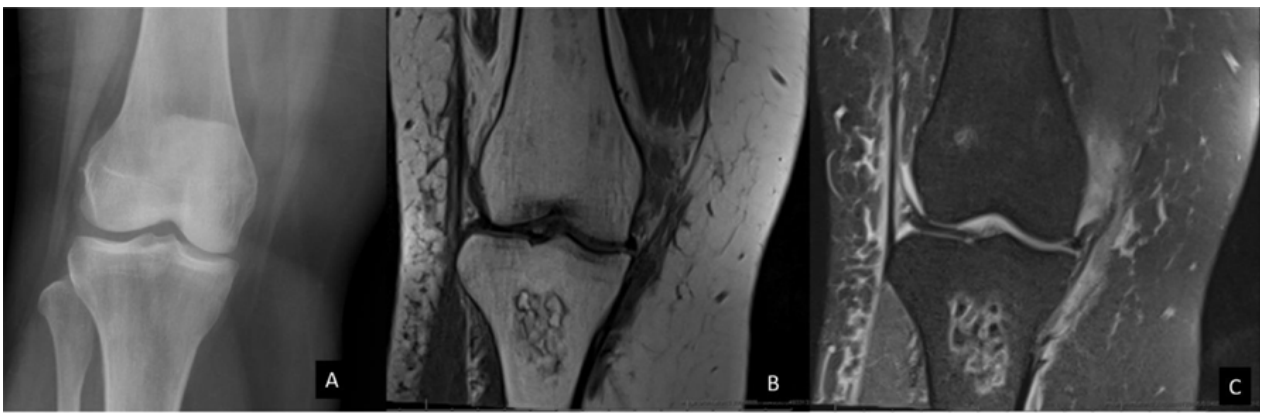
Three years after initial presentation, in February of 2019, the patient presented with new onset severe lower back pain of approximately one month's duration. In comparison to initial normal plain radiographs of the spine, L1- L2 intervertebral disc narrowing and adjacent vertebral sclerosis was now noted on conventional radiography suggestive of an infiltrative inflammatory process (Figure 3). MRI of the spine requested in response to the radiographic abnormality showed a spondylodiscitis at L1-L2 level with intervertebral disc space narrowing and both anterior and posterior sub-ligamentous abscess collection in keeping with a large left psoas abscess, findings very suggestive of TB of the spine and psoas muscle (Figure 3). Subsequent aspiration of the suspected psoas abscess confirmed the radiological suspicion of TB with a strongly positive aspirate for acid fast bacilli, and on culture was found to be resistant to both isoniazid and rifampicin. The sputum GeneXpert was also found to be positive for TB. A diagnosis of concomitant multisystem tuberculosis in a patient with known sarcoidosis of the skin, lungs and musculoskeletal systems was made.

Figure 3: A. Plain radiograph of lumbosacral spine showing L1-L2 intervertebral disc narrowing.
B & C. T1 & T2 weighted MRI lumbosacral images showing L1-L2 spondylodiscitis



Her immunosuppressive therapy was discontinued, and she was initiated on appropriate anti-tuberculous therapy with due consideration of the confirmed resistance of the organisms and the new musculoskeletal sites involvement. She later developed new skin lesions on the anterior abdominal wall, clinically suspicious for sarcoid and histologically confirmed as sarcoid when non-caseating granulomas were observed. These lesions were complicated by opportunistic fungal infection and ulceration resulting in significant distress to the patient. In addition, she developed a painful, tender right knee with inability to weight bear. A plain radiograph of the knee region appeared normal. Subsequent MRI revealed bone marrow edema, cortical bone lesions with sparing of the adjacent joint suggestive of bone sarcoidosis. Evident X-ray/MRI discrepancy was also in-keeping with sarcoidosis, and atypical for TB of the long bones (Figure 4).

Figure 4: **A**. Plain radiograph of the right knee with no significant findings. **B & C**. T1 & T2 weighted MRI images of the right knee showing proximal tibial lesions consistent with inflammatory lesions of bone



The patient was now acutely ill, metabolically difficult to control, bed-bound and with a high thrombo-embolic risk. The latter was addressed with prophylactic subcutaneous enoxaparin injections. Her clinical condition steadily declined. She suffered from new onset seizures, a focal lesion in keeping with either a tuberculoma or a vascular event was noted on CT scan of the brain and the patient unfortunately demised soon thereafter following a cerebrovascular event.

Discussion

The combination of tuberculosis and sarcoidosis in the same patient is a rare occurrence termed by some authors as "Tubercular Sarcoidosis"[1,2]. This term was later refuted owing to the lack of evidence [3]. The potential combination of these diagnoses has been described to occur in three different patterns which includes a patient with previous TB that later develops sarcoidosis, chronic sarcoidosis that later develops TB, or the co- existence of TB and sarcoidosis[1]. Our index case demonstrated features of the second pattern. Our index case was initially found to have sarcoidosis, and later demonstrated features of concurrent TB and sarcoidosis.

Sarcoidosis is an inflammatory granulomatous disease that rarely involves the skeletal system. Usually when the skeletal system is involved, it is limited to the phalanges of the hands and feet[4]. The incidence of sarcoidosis is said to be approximately 10 – 14 per 100 000 people per year, and the skeletal involvement is approximately 14% among all affected individuals[5]. Sarcoidosis and TB are closely related in many ways from pathophysiology, to clinical and radiological presentation, making it difficult to distinguish between the two, especially in a TB endemic region[6].

TB patients and in particular patients with extra-pulmonary TB, have an 8-fold higher risk of developing sarcoidosis when compared to non-TB individuals. On the other hand, sarcoidosis patients have a 2-fold risk of developing TB when compared with non-sarcoid individuals[7]. It has therefore been suggested that TB poses a bigger risk factor for subsequent sarcoidosis than vice versa[5]. A recent meta-analysis indicated the possibility of some insoluble mycobacterial antigens to be responsible for the type IV hypersensitivity immune response in the pathogenesis of sarcoidosis[8]; hence some authors believe that TB and sarcoidosis are possibly a spectrum of one disease[9].

Although these granulomatous diseases share some similarities in the pathophysiology, the therapeutic strategies are very different. It is therefore imperative to differentiate between these two conditions, especially in a TB endemic region since the immunosuppressive therapy used in sarcoidosis can predispose the host to TB infection[2]. Biopsies can differentiate between the two conditions, recognizing TB by its caseating granulomas while sarcoid lesions have non-caseating granulomas. At times this simple differentiation is not easy to ascertain, and in such a case *Mycobacterium* DNA detection with polymerase chain reaction (MTB-PCR) or the identification of acid-fast bacilli becomes the key in making the diagnosis of TB[10].

Molecular detection (PCR) of *Mycobacterium* species (16S RNA, IS6110, and rpoB sequences) on sarcoidosis tissue specimen in comparison with control tissue specimen revealed presence of *Mycobacterium* molecules. 16S RNA and rpoB sequences were amplified from 60% of all samples in a frequency of 48% and 24% of samples respectively (p=0.00002), and not amplified from any of the control specimens[11]. In this study, *Mycobacterium* other than TB (MOTT) were also identified including *M. gordonae*, and *M. kansasii*[11]. Evidently the clinical, histological and radiological differentiation of TB from sarcoidosis will remain a challenge since the overlap and co-existence of these entities extends to a molecular level.

There are no pathogmonic radiological features of musculoskeletal sarcoidosis described in literature, however there are some common radiological features described in various case reports. X-ray/MRI discrepant findings on large bones is described, whereby plain radiographs usually appear without any evidence of bone or soft tissue involvement, conversely on MRI bone lesions may resemble metastasis. Furthermore, bone marrow involvement and soft tissue lesions become evident on MRI[12]. Juxta-articular TB osteomyelitis is often associated with florid synovitis seen as low to intermediate T2 weighted signal intensity on MRI. Additional MRI features include bone marrow edema, cortical erosions, soft tissue swelling and abscess formation[13].

Conclusion

In a TB endemic region such as South Africa, making a diagnosis of TB is a daily routine in clinical practice. However, a diagnostic error of assuming that disseminated granulomatous lesions equates disseminated TB in immunocompromised hosts should be avoided. A combined diagnosis of skeletal TB and sarcoidosis should be considered in the differential diagnosis of uncertain cases.

Learning points

(i) Concomitant skeletal TB and sarcoidosis, although uncommon should be considered in immunocompromised patients with skeletal granulomatous lesions, and non-confirmatory investigations for TB.
(ii) Tissue biopsies can yield non-conclusive results in the attempt to differentiate between TB and sarcoidosis.
(iii) Skeletal MRI is a useful radiological diagnostic modality that can assist as an additional data point in differentiating between sarcoidosis and TB.

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