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Case Report

Internal Medicine Section

A Case of Renal Sarcoidosis: A Diagnostic Dilemma

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ABSTRACT

Sarcoidosis is a multi-system disease of unknown aetiology, characterised by non-caseating granulomas. It can involve any organ in the body, but commonly affects the lungs and lymph nodes. The worldwide prevalence of sarcoidosis is 20-60 per/100,000 and people, while in India, it is 61.2 per 100,000. The probable cause is an inflammatory response triggered by various environmental agents in genetically sensitive individuals. Approximately one-third of patients with sarcoidosis remain asymptomatic. Typical symptoms include non-specific pulmonary symptoms such as cough, dyspnoea and chest pain. Cutaneous or ocular manifestations may include malar rash, erythema nodosum, keratoconjunctivitis, anterior uveitis and chorioretinitis. The presence of hilar lymphadenopathy on chest X-ray is highly suggestive of sarcoidosis. In this case, a 68-year-old female patients, presented with complaints of anorexia and fatigue for the past three months. She was found to have anaemia, hypercalcaemia, and abnormal renal function. Abdominal ultrasonography (USG) showed normal findings. The patient was initially evaluated for Tuberculosis (TB) and started on empirical Anti-Tubercular Therapy (ATT). However, as the patient did not show any improvement, further evaluation was conducted, leading to a diagnosis of sarcoidosis. Treatment options for sarcoidosis include systemic steroids, immunosuppresants, and cytotoxic drugs. Biologics such as anti-Tumour Necrosis Factor (TNF) agents (etanercept, golimumab, and infliximab) have also been considered in the treatment. Sarcoidosis can present a diagnostic dilemma as seen in this patient who initially had features resembling disseminated TB. This highlights the importance of strong clinical suspicion by the treating physician and thorough evaluation.

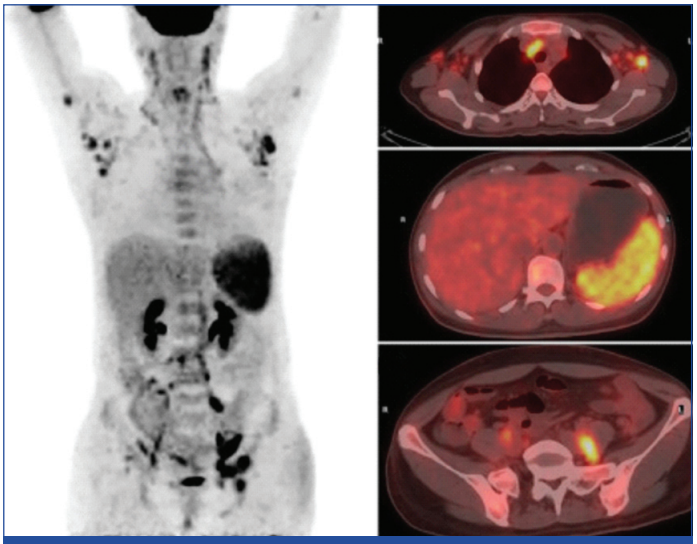
Keywords: Granuloma, Hypercalcaemia, Ocular manifestations, Pulmonary symptoms

CASE REPORT

A 68-year-old female patient, presented to the outpatient department with complaints of anorexia and fatigue for the past three months. She reported worsening fatigue and difficulty in performing daily activities. Over the last month, she experienced occasional dizziness and also complained of loss of appetite. There was no history suggestive of weight loss or fever. The patient had a known history of type 2 diabetes mellitus for 30 years and systemic hypertension for 20 years, managed with oral medications. There was no significant family history.

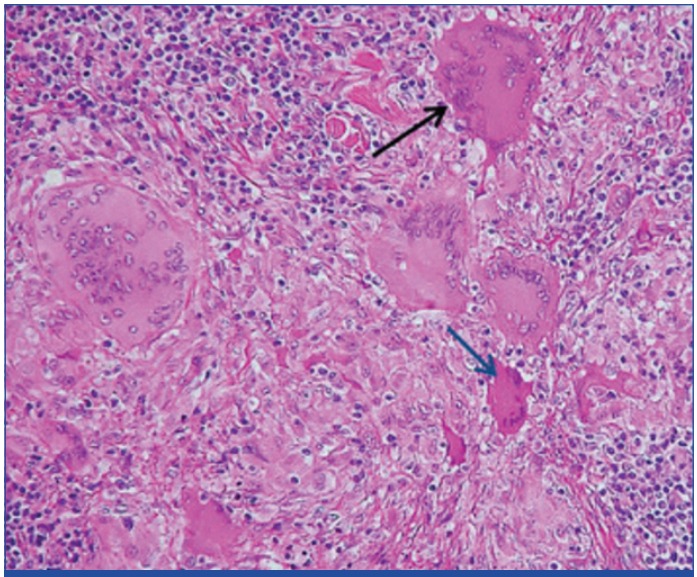
On physical examination, the patient was normothermic, normotensive with regular, normovolemic pulse rate of 80 bpm. She was afebrile. Pale palpebral conjunctiva, bilateral pitting pedal oedema up to the knee, and left inguinal lymphadenopathy were observed. Fundoscopy showed no signs of retinopathy. Examination of the cardiovascular system revealed normal heart sounds without murmurs. Bilateral vesicular breath sounds without added sounds were noted during respiratory system examination. Abdominal examination showed no hepatosplenomegaly or tenderness. A provisional diagnosis of anaemia under evaluation was made, and further investigations were initiated.

Laboratory investigations revealed elevated serum creatinine levels (2.3 mg/dL), hypercalcaemia (13.1 mg/dL), and anaemia (hemoglobin - 9.5 mg/dL). Urine analysis showed 1+ proteinuria on dipstick testing, with no red blood cells (RBCs) or white blood cells (WBCs) observed on microscopy. Due to persistent normocytic normochromic anemia and mildly elevated erythrocyte sedimentation rate (ESR) of 45 mm/hr, serum protein electrophoresis was performed, which indicated an elevation in the alpha 2-beta globulin fraction and hypergammaglobulinemia. Abdominal ultrasound was conducted to rule out kidney disease and showed normal findings. Positron Emission Tomography-Computed Tomography (PET-CT) revealed bilateral axillary, inguinal, retro-peritoneal, and parotid lymphadenopathy [Table/Fig-1]. A biopsy of the left inguinal lymph node demonstrated revealed chronic granulomatous lymphadenitis with the presence of Langerhans giant cells [Table/Fig-2]. Bone marrow aspiration revealed non-caseating granulomas [Table/Fig-3]. Sarcoidosis was suspected as the diagnosis.

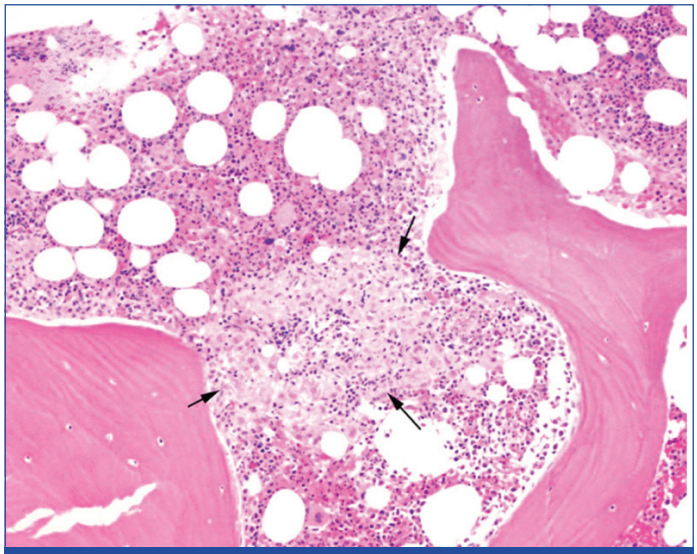


[Table/Fig-1]: PET-CT scan showing bilateral axillary, inguinal, retro-peritoneal and parotid lymphadenopathy.

The patient was initiated on anti-tubercular therapy (ATT), including Tablet(Tab.) Isoniazid 300 mg/day, Tab Rifampin 600 mg/day, Tab Pyrazinamide 1500 mg on alternate days, and Tab Ethambutol 800 mg on alternate days with renal dose modification. ATT was continued for one month. Other diseases presenting with chronic granulomatous lymphadenitis were also considered. However, hypercalcaemia and renal dysfunction did not improve with empirical ATT. Hypercalcaemia was refractory to therapy, which included hydration and other supportive measures. The Cartridge-Based Nucleic Acid Amplification Test of the sample tested negative for



[Table/Fig-2]: Lymph node biopsy revealed chronic granulomatous lymphadenitis with presence of Langerhan's giant cells.



[Table/Fig-3]: Bone marrow aspiration showing non caseating granuloma in bone marrow.

Mycobacterium TB. Histopathologically, the lymph node showed features suggestive of granulomatous lymphadenitis. Sarcoidosis In view of granulomatous lymphadenitis associated with hypercalcemia and renal failure. Sarcoidosis was suspected, serum ACE levels sent and was found to be elevated (159 u/l) [1].

The diagnosis of sarcoidosis was made based on the clinical scenario, supported by of biochemical evidence of elevated serum ACE levels (159 u/l). Oral prednisolone was started at 10 mg (tid) and later tapered over a period of six weeks, resulting in improved laboratory parameters for the patient. [Table/Fig-4] depicts comparative data of investigations before and after starting steroids. The response to steroids can be considered strong evidence of sarcoidosis.

Investigations	Before treatment	After treatment
Haemoglobin	9.5 gm/dL	11 gm/dL
Serum creatinine	2.3 mg/dL	1.4 mg/dL
Serum calcium	13.1 mg/dL	11 mg/dL

[Table/Fig-4]: Investigations before and after treatment.

DISCUSSION

Sarcoidosis is a multisystem inflammatory disorder of unknown aetiology that affects multiple organs. The clinical, radiological, and histopathological similarities between sarcoidosis and tuberculosis pose a challenge for physicians in differentiating the diseases. Kidney involvement occurs in less than 5% of cases [2]. The worldwide prevalence of sarcoidosis is 20-60/100,000, while in India, it is 61.2/100,000 [3]. Approximately one-third of patients remain asymptomatic. Common pulmonary symptoms include cough, dyspnoea, and chest pain. Cutaneous or ocular manifestations may include malar rash, erythema nodosum, keratoconjunctivitis, anterior uveitis, and chorioretinitis. The presence of hilar lymphadenopathy on chest X-ray raises suspicion of sarcoidosis. The exact cause of sarcoidosis is unknown. Advanced imaging modalities such as PET scan using 18FDG or 18FMT (fluoromethyl-tyrosine) can be useful, with 18FMT being highly specific for aiding diagnosis of sarcoidosis [4]. Most patients experience remission and do not require aggressive therapy.

Histopathologically, sarcoidosis and tuberculosis are characterised by granulomatous inflammation. The primary causes of granulomatous inflammation in sarcoidosis are believed to be a chronic, poorly degradable unknown antigen and a prolonged host response. In countries with a high burden of tuberculosis like India, the uncommon manifestations of tuberculosis may be more common in sarcoidosis. Recent studies suggest that mycobacterial antigens may be the triggering agents in some sarcoidosis patients, with stronger evidence from countries with a high burden of tuberculosis. Tuberculosis can also occur as a complication of treatment in sarcoidosis treatment, and the two conditions can rarely coexist [5].

In 1939, Harrell GT and Fisher S first described hypercalcaemia in sarcoidosis [6]. Hypercalcaemia occurs due to increased activity of activated macrophages within the granulomas. These macrophages express 1-alpha hydroxylase activity, leading to the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol. Other mechanisms for hypercalcaemia in sarcoidosis include the expression of Parathyroid Hormone-related Protein (PTH-rP) in sarcoid macrophages, which may exert an autocrine action of 1α-hydroxylase activity, and increased levels of serum Interferon (IFN)-γ [7]. Hypercalcaemia can be present in 10-17% of sarcoidosis patients [8]. Renal failure secondary to hypercalcaemia is seen in 1-2% of sarcoidosis cases and is likely the cause of sarcoidosis associated renal dysfunction. Hypercalcaemia can lead to nephrolithiasis or nephrocalcinosis, with nephrolithiasis occurring in less than 10% of cases and nephrocalcinosis in less than 5% of cases [9]. Sarcoidosis can also cause granulomatous interstitial nephritis, which is a rare finding on renal biopsy. It is observed in up to 0.9% of native kidney biopsies and approximately 6% of biopsies with interstitial nephritis [9].

Genitourinary involvement is seen in 20-40% of extrapulmonary tuberculosis (TB) cases [10]. Renal involvement is present in 74% of cases with haematogenous spread. The spectrum of renal TB presentation includes hypercalcaemia, nephrolithiasis, nephrocalcinosis, and acute tubulointerstitial nephritis with or without granulomas [11]. Hypercalcaemia is reported in about 2-10% of patients with sarcoidosis, while hypercalciuria is even more frequent. This is rare in TB but has been infrequently reported in miliary TB [12]. In a TB-endemic country like India, distinguishing between TB and sarcoidosis is important, especially due to the different treatment regimens for these two diseases.

The treatment for sarcoidosis depends on the severity of the disease. Mild cases may not require treatment, while more severe cases may require medication to reduce inflammation and suppress the immune system. Corticosteroids are the first-line treatment for organ-threatening sarcoidosis [7]. Other treatment options include immunosuppressants, cytotoxics, and biologics such as anti-TNF agents (etanercept, golimumab and infliximab). There is currently no guideline for treatment. Based on a literature, review hypercalcaemia and hypercalciuria can be treated with corticosteroids [13]. Glucocorticoids help resolve interstitial nephritis and manage hypercalcaemia. If glucocorticoids fail, ketoconazole or hydroxychloroquine can be used. Additional immunosuppressive agents like azathioprine or mycophenolate mofetil can also be

used in sarcoidosis treatment [14]. Understanding the uncommon presentations of sarcoidosis will aid in diagnosis and appropriate management of the disease. Physicians need to be aware of these presentations to facilitate better understanding and treatment of sarcoidosis patients.

CONCLUSION(S)

The patient presented with features suggestive of disseminated tuberculosis (TB) but was ultimately diagnosed with sarcoidosis. Sarcoidosis can often pose a diagnostic challenge, as seen in this patient who had symptoms resembling disseminated TB. To avoid exacerbating any potential underlying TB infection with steroid therapy for sarcoidosis, empirical anti-TB treatment (ATT) was initiated. Corticosteroids continue to be the preferred treatment for sarcoidosis.

REFERENCES

[1] Angiotensin converting enzyme (blood) [Internet]. Rochester.edu. [cited 2023 Mar 24]. Available from: https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=167&contentid=angiotensin_converting_enzyme_blood.

[2] Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL. Harrison's principles of internal medicine. 21st ed. New York: McGraw Hill; 2022. Chapter 367,Sarcoidosis; Pp. 2829-37.

[3] Babu K. Sarcoidosis in tuberculosis-endemic regions: India. J Ophthalmic Inflamm Infect. 2013;3(1):53. Doi: 10.1186/1869-5760-3-53.

[4] Kaira K, Oriuchi N, Otani Y, Yanagitani N, Sunaga N, Hisada T, et al. Diagnostic usefulness of fluorine-18-alpha-methyltyrosine positron emission tomography in combination with 18F-fluorodeoxyglucose in sarcoidosis patients. Chest. 2007;131(4):1019-27.

[5] Gupta D, Agarwal R, Aggarwal AN, Jindal SK. Sarcoidosis and tuberculosis: The same disease with different manifestations or similar manifestations of different disorders. Curr Opin Pulm Med. 2012;18(5):506-16.

[6] Harrell GT, Fisher S. Blood chemical changes in Boeck's sarcoid with particular reference to protein, calcium, and phosphatase values. J Clin Invest. 1939;18(6):687-93.

[7] Kamphuis LS, Bonte-Mineur F, van Laar JA, van Hagen PM, van Daele PL. Calcium and vitamin D in sarcoidosis: Is supplementation safe? J Bone Miner Res. 2014;29(11):2498-503.

[8] Donovan PJ, Sundac L, Pretorius CJ, d'Emden MC, McLeod DS. Calcitriol-mediated hypercalcemia: Causes and course in 101 patients. J Clin Endocrinol Metab. 2013;98(10):4023-29.

[9] Correia FASC, Marchini GS, Torricelli FC, Danilovic A, Vicentini FC, Srougi M, et al. Renal manifestations of sarcoidosis: From accurate diagnosis to specific treatment. Int Braz J Urol. 2020;46(1):15-25.

[10] Das P, Ahuja A, Gupta SD. Incidence, etiopathogenesis and pathological aspects of genitourinary tuberculosis in India: A journey revisited. Indian J Urol. 2008;24(3):356-61.

[11] Zia Z, Iqbal QZ, Ruggiero RA, Pervaiz S, Chalhoub M. A rare case of renal sarcoidosis. Cureus. 2021;13(6):e15494.

[12] Bhalla AS, Das A, Naranje P, Goyal A, Guleria R, Khilnani GC. Dilemma of diagnosing thoracic sarcoidosis in tuberculosis endemic regions: An imaging-based approach. Part 1. Indian J Radiol Imaging. 2017;27(4):369-79.

[13] Hilderson I, Van Laecke S, Wauters A, Donck J. Treatment of renal sarcoidosis: Is there a guideline? Overview of the different treatment options. Nephrol Dial Transplant. 2014;29(10):1841-47.

[14] Al-Kofahi K, Korsten P, Ascoli C, Virupannavar S, Mirsaeidi M, Chang I, et al. Management of extrapulmonary sarcoidosis: Challenges and solutions. Ther Clin Risk Manag. 2016;12:1623-34. Doi: 10.2147/TCRM.S74476. eCollection 2016.

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