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Journal of General Medicine and Clinical Practice
Anthony Kodzo-Grey Venyo *

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Research Article

Sarcoidosis of Urinary Bladder an Update

Anthony Kodzo-Grey Venyo

Retired Urologist and Clinician, Reviewer of Articles for Journals, Medical Examiner Member of Royal College of Pathologists, London. United Kingdom.

***Corresponding Author:** Anthony Kodzo-Grey Venyo, Retired Urologist and Clinician, Reviewer of Articles for Journals, Medical Examiner Member of Royal College of Pathologists, London. United Kingdom.

Received date: December 03, 2024; Accepted date: January 17, 2025; Published date: January 28, 2025

Citation: Grey Venyo AK (2025), Sarcoidosis of Urinary Bladder an Update, *J. General Medicine and Clinical Practice*, 8(1);
DOI:10.31579/2639-4162/247

Abstract

Sarcoidosis is a multi-system granulomatous disease that is characterized by non-caseating epithelioid granulomas in association with clinical and radiological findings. The cause of sarcoidosis disease is still not certain. Recent findings had indicated that sarcoidosis is related to a chronic immune response which is caused by exposure to common environmental factors such as Propionibacterium or airborne organic or inorganic material, as well as most probably a sum of several immune system and environmental factors. Sarcoidosis affects all races and genders; nevertheless, women are 30% more likely to be affected in comparison to men and African-Americans (36/100.000) are more commonly affected than Caucasians (11/100.000) Within Europe the incidence of sarcoidosis is higher in northern countries, 20-40/100.000 at general, up to 121/100.00 in Sweden and lower in southern countries like England (5/100.000) and Spain (1.36/100.000). Japan had a reported prevalence of 0.3-1.7/100.000. It has been iterated that genetic propensity might explain the heterogeneity at appearance and the severity of the cases in different ethnic groups and races. Sarcoidosis, is usually not regarded to be a urological disease, in that sarcoidosis afflicts mostly the lungs and lymph nodes. For that reason, sarcoidosis may be overlooked when it afflicts the urinary tract. Nevertheless, urinary impairment of the disease is not rare and may lead to conditions treated by the urologist such as nephrolithiasis, lower urinary tract symptoms and urinary retention as well as recurrent urinary tract infections and haematuria. Moreover, sarcoidosis of the urinary bladder and sarcoidosis of other urinary tract organs may also produce clinical manifestations that could simulate urological disorders such as testicular nodules, renal masses, or even PET positive lymphadenopathy, leading to misinterpretations of early-stage urological malignancies, including urinary bladder cancer and urothelial tumour of the ureter causing ureteric obstruction. Sarcoidosis could affect the urinary bladder alone and cause various non-specific symptoms that simulate the manifestations of more common conditions affecting structures and organs that encompass the urinary bladder or sarcoidosis of the urinary bladder may be part of systemic sarcoidosis. Sometimes a patient may have urinary bladder symptoms that emanate from affections of nerves that supply the urinary bladder even though the urinary bladder may be found to be normal upon cystoscopy and radiology imaging but the symptoms would be proven on urodynamics studies to be related to detrusor-sphincter dyssynergia emanating from neuro-sarcoidosis and sarcoidosis of the spine. Diagnosis of sarcoidosis of the urinary bladder can be established based upon the histopathology examination features of biopsy specimens of the urinary bladder lesion.

Kew Words: sarcoidosis of urinary bladder; vesical sarcoidosis; sarcoidosis of the spine; biopsy; cystoscopy; high index of suspicion; neurogenic bladder; computed tomography scan; contrast-enhancement; urodynamics

Introduction

It has been iterated that sarcoidosis had traditionally been regarded as a pulmonary disease, which primarily afflicts young African-American females. [1] It has been pointed out that contemporary epidemiology evidence had indicated that, in fact, African-Americans have 3 to 4 times increased risk of developing sarcoidosis, which is considerably <10–17 times increased risk found in the older literature. [1] [2] In addition, it has been stated that extra-pulmonary presentations of sarcoidosis impact up to between 25% to 30% of patients, which is significantly higher than was previously thought. [1] [3] [4] It has been pointed out that whilst genitourinary (GU) tract involvement had traditionally been considered to be uncommon, the literature had indicated that the incidence of sarcoidosis may actually be considerably higher, often going undetected or manifesting with symptoms that are not immediately referable to the urinary tract.[1] [5]

It has been iterated that sarcoidosis was first described and named by Boeck in 1899 and that the name was chosen because of its close appearance, both on a gross and histopathology level, to that of sarcoma. [1] [6] It has also been iterated that since its early description, concepts of the sarcoidosis disease had broadened from those of a primary dermatology disorder to those of a systemic disease that afflicts all organ systems. It has been stated that

one review had demonstrated that 16.6% of sarcoidosis patients had extrapulmonary presentations of the disease.[1] [7] It had also been pointed out that in another review, which had evaluated 1254 cases of histologically-proven sarcoidosis, Mayock et al. [8] found one case of adrenal involvement, 54 (4.3%) cases of renal involvement, and six (1%) cases of epididymal involvement. Other involved GU organs were not delineated. They also found that the patients were 37% male and 63% female; and 30% of the patients were described as "white" and 70% as "black." The US prevalence of sarcoidosis was stated to be currently estimated to be 10–14/100,000 for Caucasians and 34–65/100,000 for African-Americans. It has been iterated that African-American females between 30 years and 39 years of age comprised the largest group of individuals with sarcoidosis, which accounts for an estimated prevalence of 107/100,000. [1] [8] [9]

It has been pointed out that the aetiology of sarcoidosis has remained poorly understood, but it is widely conjectured to be a disease of activated T-cell lymphocytes. [1] It has furthermore been pointed out that granulomatous inflammation is predominantly a T-helper 1 response that is mediated by a complex network of lymphocytes, macrophages, and cytokines, and that the pathogenesis of progression to chronic, potentially fibrotic forms, is not clear but may involve apoptotic mechanisms, loss of regulatory responses, or a persistent, uncleared antigen. [1] [8] Hypercalcemia, which is conjectured to be due to its influence upon 1, 25 hydroxy-vitamin D, is present in between 5% to 10% of all cases of sarcoidosis. [1] [8] It has been iterated that familial clusters support some level of genetic involvement, possibly related to T-cell function regulation in sarcoidosis and that patients with particular human leukocyte antigen alleles may have increased susceptibility. [1] [8] In addition, it has been iterated that there had also been some evidence, based upon the presence of mycobacterial DNA sequences within tissue specimens, of an infectious aetiology, as well. [1] [8] Furthermore, it has been iterated that in addition to the direct tissue-related effects of GU organ involvement, sarcoidosis is significant for its ability to simulate other diseases, such as cancer, often making definite diagnosis difficult or confusing as well as it has been stated that sarcoidosis has truly taken the role of Grand Imitator from syphilis and tuberculosis in the 21st century, and in fact, sarcoidosis be associated with several cancers, such as carcinoma of lung, pancreas, liver, colon, breast, cervix, ovary, skin, and non-Hodgkin's lymphoma. [1] It has in addition been stated that one report had suggested a 30% increase in cancer incidence in patients with sarcoidosis. [10]

Sarcoidosis of the urinary bladder has apparently not been covered extensively in most books of medicine, surgery and urology and it would be envisaged that the majority of clinicians throughout the world would not be familiar with the diagnostic features of sarcoidosis. The ensuing chapter contains an update on sarcoidosis of the urinary bladder which has been divided into two parts: (A) Overview, and (B) Miscellaneous narrations and discussions from some case reports, case series, and studies related to sarcoidosis of the urinary bladder.

Aim

To provide an update on sarcoidosis of the urinary bladder.

Method

Internet databases were searched including: Google; google scholar; yahoo; and PUBMED. The search words that were used included: Sarcoidosis of the bladder; urinary bladder sarcoidosis; and vesical sarcoidosis. Fifty-four (54) references were identified which were used to write the chapter on sarcoidosis of the urinary bladder which has been divided into two parts: (A) Overview, and (B) Miscellaneous narrations and discussions from some case reports, case series, and studies related to sarcoidosis of the urinary bladder.

Results

[A] Overview

Definition, General statements, Practice Essentials. [11]

Sarcoidosis has been defined as a multi-system inflammatory disease of unknown aetiology which predominantly affects the lungs and intrathoracic lymph nodes and is manifested by the presence of non-caseating granulomas (NCGs) within afflicted organ tissues of the body. [11]

- It has been iterated that Sarcoidosis is characterized by a seemingly exaggerated immune response against a difficult–to-discern antigen. [11] [12]
- The age-adjusted incidence of sarcoidosis has been stated to be 11 cases per 100,000 population in whites but 34 cases per 100,000 population in African Americans. [11] [12]

Signs and symptoms

The presenting signs and symptoms in sarcoidosis are stated to vary depending upon the extent and severity of the organ which is involved by sarcoidosis as follows**: [**11] [12]

- Sometimes sarcoidosis may be asymptomatic, and incidentally identified upon chest radiography images in about 5% of cases. [11]
- It has been stated that in 45% of cases, sarcoidosis may present with systemic complaints including: fever, and anorexia in 45% of cases. [11]
- It has been documented that sarcoidosis in 50% of cases does manifest with pulmonary complaints including: dyspnoea on exertion, cough, chest pain, and haemoptysis on rare occasions. [11]
- It has been stated that at times, sarcoidosis may present as neuro-sarcoidosis including: cranial neuropathies, leptomeningeal disease, intraparenchymal lesions, and myelitis, which does occur in between 5% to 10% of cases. [11] [13]
- It has additionally been stated that in sarcoidosis, Löfgren syndrome which manifests with fever, bilateral hilar lymphadenopathy, and poly-arthralgias does occur and this sarcoidosis affliction is common in Scandinavian patients, but it is not common in African-American and Japanese patients. [11]

The pulmonary findings on physical examination of patients affected by sarcoidosis had been summarized as follows: [11]

- Usually there has tended to be normal pulmonary examination of patients afflicted by sarcoidosis. [11]
- In some cases of sarcoidosis, clinical respiratory tract examination of affected individuals might demonstrate audible crackles. [11]
- In some individuals affected by sarcoidosis, their clinical examination may demonstrate exertional oxygen desaturation. [11]

It has been stated that dermatology manifestations of sarcoidosis may include the following: [11]

- Erythema nodosum. [11]

- A lower-extremity panniculitis with painful, erythematous nodules that often tend to be seen in association with Löfgren syndrome. [11]
- Lupus pernio, which is documented to be the most specific associated cutaneous lesion of sarcoidosis. [11]
- Violaceous rash on the cheeks or nose tend to be common in cases of sarcoidosis. [11]
- Maculopapular plaques tend to be visualised in some cases of sarcoidosis which has been stated to be an uncommon feature of sarcoidosis. [11]

It has been iterated that ocular involvement, in cases of sarcoidosis which may lead to blindness if untreated, may present as follows: [11]

- Anterior or posterior granulomatous uveitis, which is most frequently seen. [11]
- Conjunctival lesions as well as scleral plaques. [11]

Other possible presentations of sarcoidosis do include the ensuing: [11]

- Osseous involvement. [11]
- Heart failure from cardiomyopathy may be encountered on rare occasions. [11]
- Heart block and sudden death of the sarcoidosis affected individual. [11]
- On rare occasions lymphocytic meningitis of the sarcoidosis afflicted individual. [11]
- On rare occasions, individuals who are affected by sarcoidosis may manifest with stroke, seizure, intracranial mass, hypopituitarism, neuropsychiatric symptoms, and encephalopathy and all these manifestations are stated to be rare. [11]

Diagnosis

The radiology-image studies for sarcoidosis had been summarized as follows: [11]

- Chest radiography: It has been iterated that chest radiograph is central to the evaluation of sarcoidosis. [11]
- Routine chest computed tomography (CT): It has been iterated that the undertaking of computed tomography of the thorax adds little to radiography findings. [11]
- High-resolution CT (HRCT) scanning of the chest: It has been iterated that high-resolution CT (HRCT) scan may be helpful, in that it does identify active alveolitis versus fibrosis, and findings correlate with biopsy yield. [11]
- Gallium scans: It has been pointed out that Gallium scans are undertaken infrequently and that Gallium scan has a-low sensitivity and specificity, but may be helpful when the clinical picture remains confusing despite histology examination evidence of non-caseating granulomas, for example in differentiating chronic hypersensitivity pneumonitis from sarcoidosis. [11]

Staging of sarcoidosis had been summated as follows: [11]

- Stage 0: Normal chest radiographic findings
- Stage I: Bilateral hilar lymphadenopathy
- Stage II: Bilateral hilar lymphadenopathy and infiltrates
- Stage III: Infiltrates alone
- Stage IV: Fibrosis

It has been stated that pulmonary function tests and a carbon monoxide diffusion capacity test of the lungs for carbon monoxide (DLCO) are used routinely in evaluation and follow-up of individuals afflicted by sarcoidosis, [11] and that some of the possible findings of the tests do include the following: [11]

- An isolated decrease in DLCO is the most common abnormality found in cases of sarcoidosis. [11]
- A restrictive pattern is seen in patients with more advanced pulmonary sarcoidosis disease. [11]
- About 15% to 20% of sarcoidosis patients are iterated to have obstruction. [11]
- It has been iterated that cardiopulmonary exercise testing is a sensitive test for the identification and quantification of the extent of pulmonary involvement. [11]
- Cardiopulmonary exercise testing also may indicate cardiac involvement that otherwise is not evident. [11]
- Impaired heart rate recovery during the first minute ensuing exercise had been demonstrated to be an independent predictor for cardiovascular and all-cause mortality, [14] and it might identify patients who are at high risk for the development of arrhythmias and sudden death.[15]
- It had been advised that all patients with sarcoidosis should have an annual electrocardiogram, and that patients who report palpitations should have a thorough evaluation with at least Holter monitoring.[11]
- Diagnosis of sarcoidosis requires biopsy in most cases. [11]
- Endobronchial biopsy via bronchoscopy is often undertaken. [11] The yield is stated to be high; and it has been iterated that results of the biopsy may be positive even in patients with normal chest radiographs. [11] The central histopathology examination finding is the presence of non-caseating granulomas with special stains negative for fungus and mycobacteria. [11]

Routine laboratory evaluation is stated to be often unrevealing, but possible abnormalities include the following: [11]

- Hypercalcemia (about 10-13% of patients)
- Hypercalciuria (about a third of patients)
- Elevated alkaline phosphatase level
- Elevated angiotensin-converting enzyme (ACE) levels.

Management

The management of sarcoidosis has been summarized as follows: [11]

It has been iterated that non-steroidal anti-inflammatory drugs (NSAIDs) are indicated for the treatment of arthralgias and other rheumatic complaints.

[11] It has also been stated that patients with stage I sarcoidosis often do require only occasional treatment with NSAIDs. [11]

Treatment in sarcoidosis patients with pulmonary involvement has been summated as follows:

- Asymptomatic patients may not require treatment at all and would need to be observed.
- In sarcoidosis patients with minimal symptoms, serial re-evaluation is important. [11]
- Treatment is indicated for sarcoidosis patients with significant respiratory symptoms. [11]
- Corticosteroids can produce small improvements in the functional vital capacity and in the radiographic appearance in sarcoidosis patients with more severe stage II and III disease. [11]

For extrapulmonary sarcoidosis involving such critical organs such as the heart, liver, eyes, kidneys, or central nervous system, corticosteroid therapy is stated to be indicated. [11] It has been iterated that topical corticosteroids are effective for ocular disease. [11] For pulmonary sarcoidosis disease, it has been iterated that prednisone is generally given daily and then tapered over a 6-month course. It has also been stated that high-dose inhaled corticosteroids could be an option, particularly in sarcoidosis patients with endobronchial disease.

Common indications for non-corticosteroid agents in cases of sarcoidosis had been stated to include the ensuing: [11]

- Steroid-resistant disease
- Intolerable adverse effects of steroids
- Patient desire not to take corticosteroids

Non-corticosteroid agents that tend to be used in sarcoidosis include the ensuing: [11]

- Methotrexate (MTX) had been a successful alternative to prednisone. [11]
- Chloroquine and hydroxychloroquine had been used for cutaneous lesions, hypercalcemia, neurologic sarcoidosis, and bone lesions. [11]
- Chloroquine had been found to be effective for acute and maintenance treatment of chronic pulmonary sarcoidosis. [16] [17] Cyclophosphamide had been rarely used with modest success as a steroid-sparing treatment in patients with refractory sarcoidosis. [18] [19]
- It has been iterated that Azathioprine is best used as a steroid-sparing agent. [11] [20]
- It has been iterated that Chlorambucil might be beneficial in patients with progressive disease unresponsive to corticosteroids or when corticosteroids are contraindicated. [11] [21]
- It had been stated that cyclosporine might be of limited benefit in skin sarcoidosis or in progressive sarcoid resistant to conventional therapy. [11] [22]
- It has been documented that Infliximab, [23] [24] and thalidomide, [25] [26] had been utilised for the treatment of refractory sarcoidosis, particularly for cutaneous disease, as well as for the long-term management of extrapulmonary sarcoidosis. [27]
- It had furthermore, ben stated that Infliximab appeared to be an effective treatment for patients with systemic manifestations such as lupus pernio, uveitis, hepatic sarcoidosis, and neuro-sarcoidosis. [11]

It had also been iterated that for sarcoidosis patients with advanced pulmonary fibrosis from sarcoidosis, lung transplantation remains the only hope for long-term survival and that indications for transplantation include either or both of the following. [28]:

- Forced vital capacity below 50% predicted [11]
- Forced expiratory volume in 1 second below 40% predicted. [11]

[B] Miscellaneous Narrations and Discussions from Sarcoidosis of The Urinary Bladder

Droessler et al. [29] reported a 33-year-old African American female, who was a former smoker, who had presented in the emergency room (ER) with a 1-month history of recurrent urinary tract infections (UTI), severe dysuria, visible haematuria, a painful vagina, and increasing difficulty emptying the bladder. She had been seen by an outpatient gynaecologist in the previous month and she was diagnosed with a UTI, which was confirmed by dipstick urinalysis and microanalysis, and which was treated with ciprofloxacin. It was noted during that visit that there was an abnormal palpable mass of the urethra, and she was referred to a urologist. She did not follow up with a urologist, and over the next month the periurethral pain gradually worsened, despite antibiotic treatment, which prompted her to go to the ER. She had a history of sarcoidosis, which was diagnosed 4 months earlier via the undertaking of bronchoscopy and mediastinal lymph node biopsy, but she was not undergoing treatment and was being monitored by a respiratory physician and nephrologist. Her family history was significant for sarcoidosis in her sister and breast cancer in her maternal aunt.

Hayashida, et al. [30] made the ensuing iterations:

- Sarcoidosis is a multisystem inflammatory disorder, which could affect any organ; nevertheless, ureteric involvement of sarcoidosis is extremely rare with only four cases reported in the literature up to 2020, all of which were diagnosed with surgical ureteral resection including a nephroureterectomy.
- They had reported the first case of sarcoidosis of the ureter, which was controlled with medical treatment where a differential diagnosis was undertaken based upon the diagnostic clue of hypercalcemia. A definitive diagnosis was made without surgical resection of the ureter.

Hayashida, et al. [30] reported a 60-year-old man, who presented with anorexia and weight loss. His blood tests showed renal dysfunction and hypercalcemia. He had computed tomography scan which showed left hydronephrosis which was associated with left lower ureteral wall thickening, which demonstrated high signal intensity upon diffusion-weighted magnetic resonance imaging. Similarly, Hayashida, et al. [30] identified a urinary bladder tumour during cystoscopy, and a 2-cm-long stenosis which was demonstrated by retrograde ureterogram; therefore, ureteral cancer was suspected. Meanwhile, taking into consideration the clinical implication of hypercalcemia, a differential diagnosis of sarcoidosis was established based upon elevated levels of sarcoidosis markers. Fluorodeoxyglucose positron emission tomography demonstrated fluorodeoxyglucose accumulation in the left lower ureter, skin, and muscles, indictive of ureteric sarcoidosis with systemic sarcoid nodules. For a

definitive diagnosis, transurethral resection of the bladder tumour (TURBT) and ureteroscopy biopsy were undertaken. Histopathology examination of the specimens revealed ureteric sarcoidosis with bladder urothelial carcinoma. Following an oral administration of prednisolone, his hypercalcemia instantly resolved, the renal function immediately improved, and the left ureteral lesion showed complete resolution with no recurrence.

Hayashida, et al. [30] made the ensuing conclusions

- In their reported case, the co-occurrence of ureteral lesion with a urinary bladder tumour had evoked a diagnosis of ureteral cancer.
- Nevertheless, considering a case of ureteral lesion complicated with hypercalcemia, assessment for differential diagnosis was undertaken based upon the calcium metabolism and sarcoidosis markers.
- In cases of suspected ureteric sarcoidosis from the assessment, pathological evaluation with ureteroscopy biopsy should be undertaken to avoid the undertaking of nephroureterectomy.

La Rochelle et al. [31] described the urological manifestations of sarcoidosis and how the disease may affect the management of multiple urological conditions. La Rochelle et al. [31] undertook a PubMed® search using the query sarcoidosis and multiple urological terms. La Rochelle et al. [31] reported the ensuing results:

- Sarcoidosis is a disease which has variable presentations.
- There is often genitourinary involvement in sarcoidosis which is clinically silent.
- Nevertheless, sarcoidosis may cause symptoms, such as nephrolithiasis, which are sometimes the first presentation of the disease.
- Renal function might be affected by sarcoidosis, and appropriate recognition and treatment may avert progressive functional decline.
- The presence of sarcoidosis might also confound the diagnosis and staging of various urological malignancies, particularly renal and testicular carcinoma.

La Rochelle et al. [31] made the ensuing conclusion and advise:

- Urologists should be aware of the urological manifestations of sarcoidosis to avoid misdiagnoses and the over staging of urological cancers, and to identify sarcoidosis when it is an underlying cause of nephrolithiasis or obstructive uropathy.

Tammela et al. [32] reported a case of sarcoidosis of the urinary bladder in a woman with a known systemic involvement. The sarcoidosis lesion improved and her ureteral obstruction was relieved after transurethral resection and systemic corticosteroid treatment. Tammela et al. [32] concluded that sarcoidosis and malacoplakia are believed to represent distinct disease processes in the bladder.

Fukutani et al. [33] reported a 75-year-old woman with transitional cell carcinoma of the renal pelvis, who was revealed to have sarcoid granulomas within the kidney as well as in the renal pedicle lymph nodes. In addition, non-caseating granulomas had been found within the pelvic lymph nodes in a histological study following previous total cystectomy for urinary bladder cancer.

Sakakibara et al. [34] reported a case of neuro-sarcoidosis in which urodynamic studies had demonstrated neurogenic bladder dysfunction. Sakakibara et al. [34] reported a 30-year-old man, who began to have slowly progressive gait ataxia of vestibular origin, deafness, and hallucination, which developed into seizure and stupor. He had computed tomography scan of his brain and magnetic resonance imaging scan which demonstrated an anteromedial frontal lobe lesion with mild ventricular enlargement. His cerebrospinal fluid examination revealed pleocytosis with raised total protein and angiotensin-converting enzyme levels. He had endoscopic lung biopsy and pathology examination of the biopsy specimen demonstrated epithelioid granuloma. He took oral prednisolone (60 mg/day) medication, which ameliorated his symptoms. After tapering his steroids, however, he developed urinary urgency, frequency, urge urinary incontinence, and a relapse of gait ataxia. He had urodynamic study which demonstrated detrusor hyperreflexia. Prednisolone treatment again improved his urinary and neurological symptoms. Sakakibara et al. [34] concluded that:

- The anteromedial frontal lobe lesion seemed to be responsible for the micturition disturbance in the patient with neuro-sarcoidosis.

Chouaib et al. [35] reported a case of spinal cord sarcoidosis in which urodynamic studies had demonstrated neurogenic bladder dysfunction. Chouaib et al. [35] reported a 56-year-old Caucasian woman, who developed progressive weakness of both lower extremities causing walking disturbance. Two months subsequently, she became unable to walk, and she gradually developed urinary urgency, nocturnal urinary frequency, and urge urinary incontinence. She had spinal MRI scan, which disclosed dorsal lesion, with atrophy of the cervical cord; she also had brain MRI scan which was normal. Her cerebrospinal fluid (CSF) upon analysis demonstrated elevated proteins. Her level of serum angiotensin-converting enzyme (ACE) level was moderately high. Her tuberculin skin test was negative. She had a scan of her thorax and abdomen and pelvis which demonstrated showed a suspicious lesion within her liver. She had draining-biopsy of the liver lesion and pathology examination of the specimen demonstrated non-caseating epithelioid granuloma. It was adjudged that the aforementioned finding had confirmed the diagnosis of spinal cord sarcoidosis. She urodynamic study which demonstrated detrusor hyperreflexia. She received prednisolone treatment, which improved her urinary and neurological symptoms. Chouaib et al. [35] concluded that:

- The spinal lesion seemed to be responsible for her voiding disturbance with spinal cord sarcoidosis.

Osanami et al. [36] made the ensuing iterations:

- Sarcoidosis affects multiple organs and exhibits diverse clinical presentations.
- Even though tubulointerstitial nephritis is a known feature of renal involvement, necrotizing vasculitis is rare.
- In addition, prostate involvement of the prostate gland with urinary retention is unusual in patients with sarcoidosis.
- They had reported a case of systemic sarcoidosis with a rare combination of presentations and different acute kidney injuries.

Osanami et al. [36] reported a 66-year-old man, who developed sudden urinary retention and fever. He was diagnosed with prostatitis and admitted to the hospital of Osanami et al. [36] An indwelling urethral catheter was inserted, and antimicrobial therapy was commenced; nevertheless, the prostatitis was refractory. He had computed tomography scan, which showed enlarged mediastinal lymph nodes. Analysis of trans-bronchoscopy lymph node and prostate biopsies demonstrated epithelioid cell granulomas, indicating systemic sarcoidosis. During the clinical course, his serum creatinine level rapidly increased to 2.36 mg/dL without

oliguria. A kidney biopsy was undertaken and pathology examination of the biopsy specimen showed tubulointerstitial injury with moderate lympho-histiocytic infiltration and small-vessel vasculitis within the interstitium. Following oral administration of 60 mg/day prednisolone, the patient's renal function immediately improved, and his urinary retention did not recur.

Osanami et al. [36] made the ensuing conclusions:

- To the best of their knowledge, this case was the first reported case of sarcoidosis with two unusual complications.
- Given its clinical course and pathology, the case is clinically valuable.

Upon reflection, a lesson that needs to be appreciated or learnt from this case report, is that a patient may at times be afflicted by sarcoidosis affecting a different organ and not the urinary bladder directly but the patient may manifest with lower urinary tract symptoms including urinary retention.

Hanif et al. [37] made the ensuing iterations:

- It had been iterated that neuro-sarcoidosis is a challenging medical condition where up to 70% of patients manifest with neurological presentations rather than already having a known systemic diagnosis. [38]
- It had been pointed out that neuro-sarcoidosis is difficult to diagnose as the disease can manifest in many different ways. [39]
- The diagnosis of neuro-sarcoidosis is stated to be usually a diagnosis of exclusion as it often masquerades as other disorders, at times creating a lengthy differential and complicated diagnosis. [40]
- There is no cure for neuro-sarcoidosis, and most patients require long-term treatment with corticosteroids.

Hanif et al. [37] reported a 55-year-old African American male, who had a medical history of substance use, cerebrovascular accident, hepatitis B, and who was recently diagnosed with right lower extremity deep venous thrombosis on anticoagulation and who had presented to the hospital with complaints of dizziness, blurry vision and left-sided weakness of one-day duration. It was noted that the patient had had many emergency department visits within the preceding one month for similar left-sided leg pain and falls. He had been treated for cellulitis and pain. This time he underwent computed tomography (CT) scan of the brain which demonstrated large areas of white matter hypodensities in bifrontal lobes as well as small areas of cortical hypodensities in the right anterior-inferior frontal lobe (see figure 1).

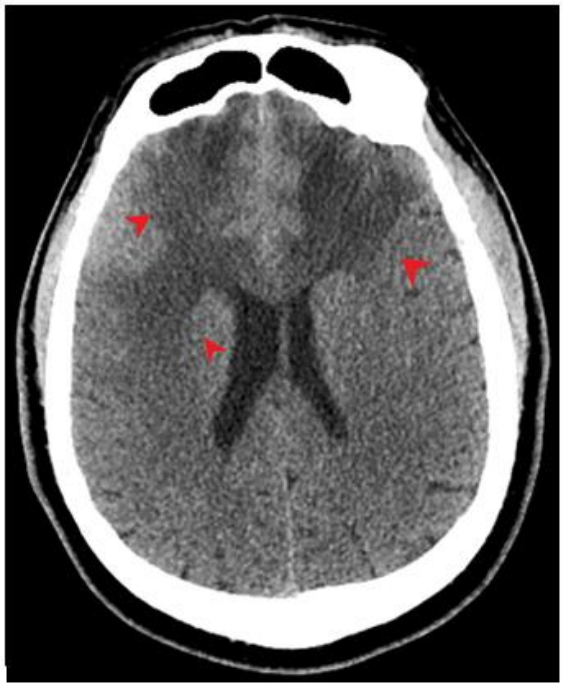

Figure 1:

CT scan of the brain (axial view), on arrival, demonstrating large areas of white matter hypodensities in the bifrontal lobes as well as small areas of cortical hypodensities in the right anteroinferior frontal lobe (arrows). Reproduced from: [37] under the Creative Commons Attribution License.

This was initially concerning for acute infarct versus subacute post-traumatic changes, which were the differential diagnose. Other possible differentials included: reversible posterior leukoencephalopathy or neoplastic process given the local mass effect. His neurological examination was non-focal and his cranial nerves II-XII were intact. A painful range of motion was identified in his lower extremity; nevertheless, his muscle strength was found to be 5/5. Additional findings upon his clinical examination included bilateral lower extremity oedema left more than right, oral thrush and right axillary lymphadenopathy. The stroke protocol was commenced, and he was admitted to the hospital. Neurology and Haematology Oncology services were consulted for further assessment. He had magnetic resonance imaging (MRI) scan of the brain with contrast, which demonstrated extensive contrast-enhancing dural nodularity along bilateral frontal convexities and anterior falx associated with extensive nodular leptomeningeal enhancement along the bilateral frontal lobes, suprasellar cistern, right sylvian fissure, and right basal ganglia with associated extensive bilateral frontal vasogenic oedema and mass effect on lateral ventricles (see figures 2, and 3).

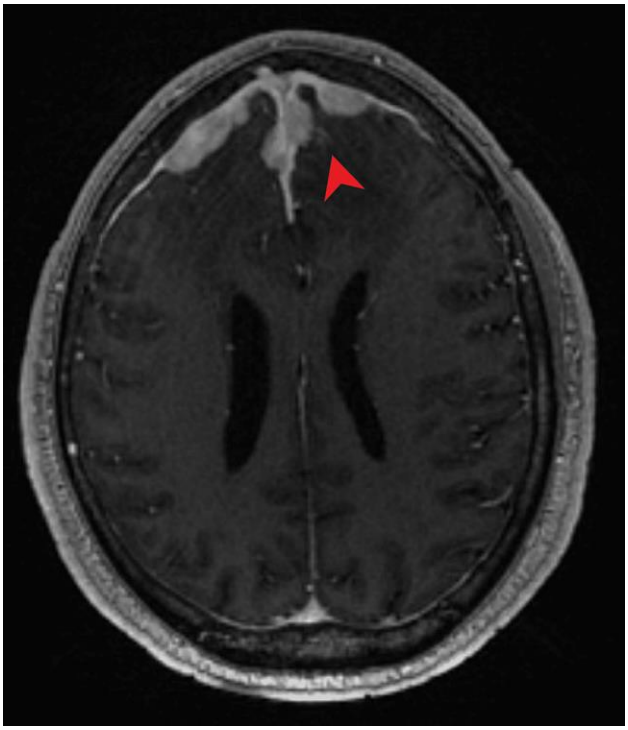

Figure 2:

Axial T1-weighted MRI of the brain with contrast showing extensive enhancing dural nodularity along bilateral frontal convexities and anterior falx (red arrow). Reproduced from: [37] under the Creative Commons Attribution License.

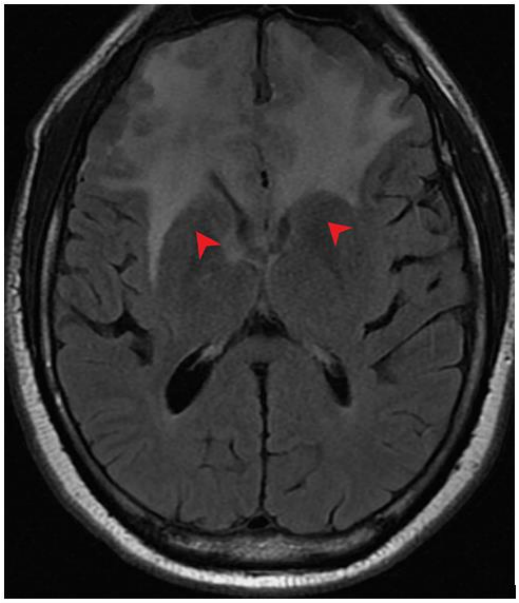

Figure 3:

Axial T1-weighted MRI of the brain with contrast revealing extensive nodular leptomeningeal enhancement along the bilateral frontal lobes, suprasellar cistern, right Sylvian fissure, and right basal ganglia with associated extensive vasogenic oedema extending to the lateral ventricles (red arrows). Reproduced from: [37] under the Creative Commons Attribution License.

The differential diagnoses were narrowed down to central nervous system (CNS) lymphoma versus neuro-sarcoidosis. In view of concerns of CNS lymphoma, steroids were initially withheld pending the results of his cerebrospinal fluid (CSF) analysis. He underwent CT scan of the thorax without contrast which demonstrated sub-centimetre mediastinal, bilateral hilar, and right axillary lymphadenopathy (see figure 4). A core needle biopsy of the largest axillary lymph node was undertaken and pathology examination of the biopsy specimen demonstrated benign and reactive areas. There was an insufficient sample for flow cytometry to be undertaken.

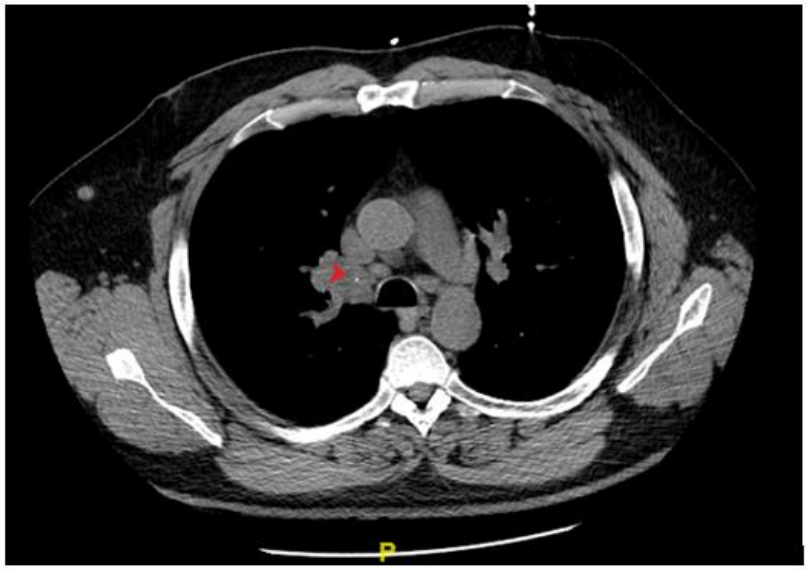

Figure 4:

Axial view of chest CT without contrast showing calcified right hilar adenopathy (arrow). Reproduced from: [37] under the Creative Commons Attribution License.

He underwent CT scan of the abdomen and pelvis with contrast for further assessment of lymphadenopathy which identified a 2.6-cm urinary bladder wall tumour, which was concerning for neoplasm. There was also bilateral iliac chain and retroperitoneal adenopathy which was suspicious for metastatic disease. He underwent trans-urethral resection of the urinary bladder tumour (TURBT). The pathology examination demonstrated revealed non-caseating granulomas (see figures 5 and 6).

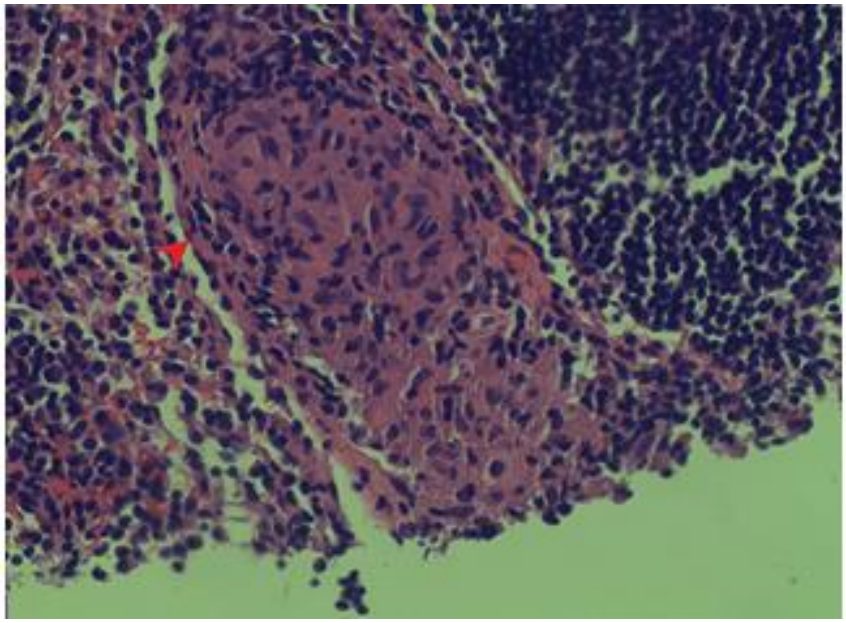

Figure 5:

Pathology of the bladder mass showing noncaseating granulomas (arrow). Reproduced from: [37] under the Creative Commons Attribution License.

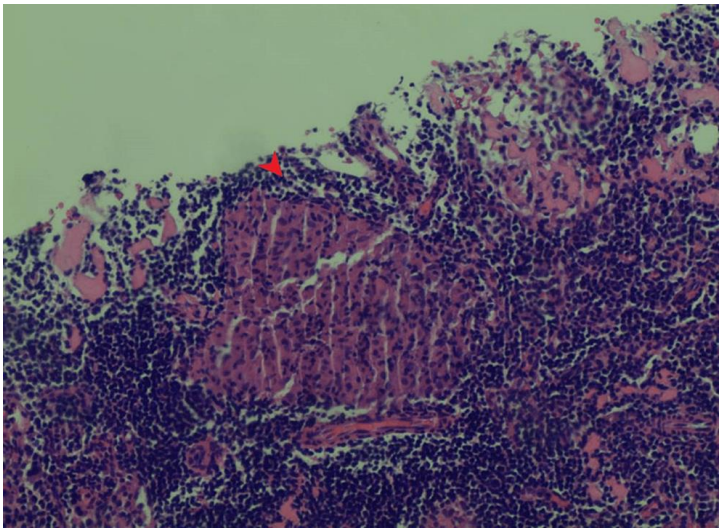

Figure 6:

Pathology of the bladder mass showing noncaseating granulomas (arrow). Reproduced from: [37] under the Creative Commons Attribution License.

On hospital day 7, he developed new-onset left-sided weakness including reduced grip strength and left-sided facial droop. He had brain radiology-imaging which showed persistent vasogenic oedema. After a discussion with all the specialists, the decision was taken to commence steroids preceding his CSF analysis. Acid-fast bacilli (AFB) stains from the axillary lymph node as well as the urinary bladder tumour upon examination were reported to be negative. At that time, a lumbar puncture was undertaken which was negative for infection or malignancy. His CSF angiotensin-converting enzyme (ACE) levels were noted to be within normal limits (see Tables 1 and 2).

Laboratory test	Result	Reference values
Treponemal-specific enzyme immunoassay	<0.2	0.0-0.9
Neisseria gonorrhoeae DNA amplification	Negative	Negative
Chlamydia trachomatis DNA amplification	Negative	Negative
EBV DNA (PCR)	Negative	Negative
CMV DNA qual (PCR)	Negative	Negative
Hepatitis Bs Ag	Positive	Negative
Hepatitis Bs Ab	0 mIU/mL	>12.0 mIU/mL
Hepatitis Bc IgM Ab	Negative	Negative
Hepatitis Be Ag	Positive	Negative
HIV 1 and 2 Ag/Ab	Nonreactive	Nonreactive

Table 1: Infectious workup.

PCR: polymerase chain reaction; Ab: antibody; Ag: antigen; EBV: Ebstein-Barr virus; CMV: cytomegalovirus; HIV: human immunodeficiency virus. **Reproduced from: [37] under the Creative Commons Attribution License.**

CSF analysis	Result	Reference values
Appearance	Clear	Clear
WBC	3	0-10/CMM
RBC	0	0-3/CMM
Neutrophils %	0	0-6%
Lymphocytes %	55	40-80%
Monocytes %	45	15-45%
Glucose	66	40-70 mg/dL
Total protein	62.5	15-45 mg/dL
Angiotensin-converting enzyme	<1.5	0.0-3.1 U/L
IgG*	7.7	0.0-10.3
Serum analysis		
IgG (serum)	2535	603-1613 mg/dL
IgA (serum)	104.1	70-400 mg/dL

IgM (serum)	<25	40-230 mg/dL
IgE (serum)	159	<100 IU/mL
Free kappa light chain, quantitative	208.7	3.3-19.4 mg/L
Free lambda light chain, quantitative	11.2	5.7-26.3 mg/L
ANA screen	Negative	Negative

Table 2: CSF and serum analysis

WBC: white blood cell; RBC: red blood cell; CSF: cerebrospinal fluid; ANA: antinuclear antibody. *IgG index was 0.4 (normal reference value 0.0-0.7). **Reproduced from: [37] under the Creative Commons Attribution License.**

He clinically improved after the commencement of steroids and he had a repeat MRI scan of the brain, which demonstrated moderate interval improvement with persistent leptomeningeal enhancement and resolution of the previously present mass effect on frontal horns. The diagnosis of neuro-sarcoidosis was favoured given bilateral hilar adenopathy on the CT scan of thorax, improvement in his radiology-imaging findings following steroid administration, and non-caseating granulomas that were found within the urinary bladder lesion. Neurosurgery and Oncology did not favour brain biopsy at that time. He was discharged home on dexamethasone with instructions to follow up with Rheumatology as an outpatient.

Hanif et al. [37] made the ensuing educative iterations:

- It has been iterated that up to 70% of patients with neuro-sarcoidosis manifest to medical care with their neurological presentations rather than already having a known systemic diagnosis. [38]
- In view of the fact that the disease can manifest in many different ways without biopsy evidence, solitary nervous-system sarcoidosis has been difficult to diagnose. [39]
- The diagnosis is usually one of exclusion as it often does masquerade as other disorders, at times creating a lengthy differential diagnoses and complicated diagnoses. [40]
- There is no cure and the majority of the patients o require long-term treatment with corticosteroids.
- Neuro-sarcoidosis exhibits variable degrees of infiltration within the brain resulting in focal or disseminated nodules or plaques affecting particularly the basal meninges.
- The granulomatous infiltration might extend into the cortex or white matter and causing parenchymal lesions. [4] [41] [42] [43] [44] This pattern which is demonstrated in radiology-imaging is generally indistinguishable from that demonstrated with tuberculosis or lymphoma with leptomeningeal involvement. [42]
- Beside parenchymal lesions and meningeal masses, hydrocephalus might also be demonstrated upon MRI scan.
- In 2018, the Neuro-sarcoidosis Consortium Consensus Group had developed a diagnostic approach for neuro-sarcoidosis, which was adapted from 1999, which described possible, probable and definite neuro-sarcoidosis. [45] [46]
- Alternative diagnoses like infection or malignancy must be exclude and the undertaking of a tissue biopsy was recommended.
- A non-neural pathology confirming systemic sarcoidosis would provide support for the diagnosis of probable neuro-sarcoidosis, whereas having a neural tissue showing non-caseating granulomas gives a definite diagnosis.
- If histology is not obtained, having at least two indirect indicators from a gallium scan, imaging of the thorax, and serum ACE is accepted as the confirmation of systemic sarcoidosis.
- Over the recent years, F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) scans had become an important tool to assess other sites of involvement in neuro-sarcoidosis and to select more surgically accessible sites for the undertaking of biopsy. [47]
- If the clinical picture is indicative of neuro-sarcoidosis but alternate diagnoses had not been excluded, then a diagnosis of neuro-sarcoidosis is thought to be possible (see table 3 and figure 7).

Diagnosis	**Criteria**
Probable	Non-neural pathology confirming systemic sarcoidosis.
Possible	The clinical picture is suggestive of neuro-sarcoidosis, but alternate diagnoses have not been ruled out and there is no systemic confirmation of sarcoidosis.
Definitive	Neural tissue showing noncaseating granulomas.

Table 3: Diagnostic criteria

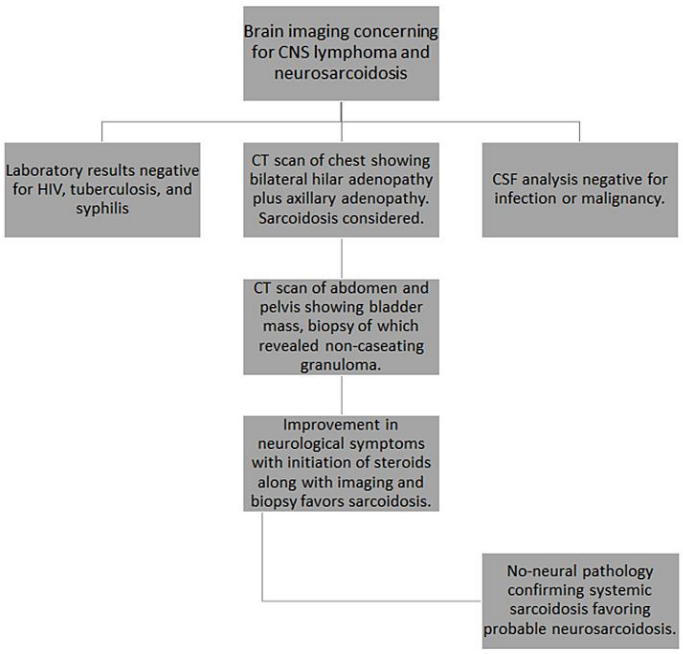

Figure 7: Diagnostic algorithm

CNS: central nervous system; CSF: cerebrospinal fluid. **Reproduced from: [37] under the Creative Commons Attribution License.**

- There are many conditions that neuro-sarcoidosis can simulate. One of them is multiple sclerosis (MS), given the radiological findings upon MRI scan besides relapsing-remitting course of the disease as well as dissemination of the MRI lesions in space and time.
- Cognitive and neuropsychiatric manifestation in the context of parenchymal brain lesions argues against MS, and certainly, coexisting peripheral nervous system involvement or myopathies are distinctive features of neuro-sarcoidosis. [46]
- Furthermore, neuro-sarcoidosis could manifest with weakness or dysarthria simulating a stroke.
- Transient ischemic attacks and ischemic stroke as am emanation of neuro-sarcoidosis had been reported. [48]
- Neuro-sarcoidosis might co-exist with multiple myeloma or might be confused with neuropathies secondary to monoclonal proliferation or paraproteinemic neuropathy.
- The contrast-enhancing parenchymal lesions might also be mistaken for neoplasms; nevertheless, the lack of central necrosis in histology differentiates neuro-sarcoidosis from malignancy.
- Central nervous system (CNS) lymphoma is another possible differential diagnosis to keep in mind.
- There had been a case reported on neurolymphomatosis simulating neuro-sarcoidosis.
- Neurolymphomatosis represents a unique subtype of extra-nodal lymphoma with localized invasion of cranial or peripheral nerves that are reported in patients with large B-cell non-Hodgkin's lymphoma. [49]
- Their reported case was not only a diagnostic challenge but also a therapeutic one in view of social constraints. The patient's comorbidities, in addition to his homelessness, made it challenging to ensure follow-up with various specialists.
- Several works of literature had demonstrated sarcoidosis to be a disease which affects those with health disparities. [50] [51]
- According to Sharp et al., "worse dyspnoea, lower health-related quality of life, and higher rates of mortality and hospitalization are more common among those who are black, female, or of low socioeconomic status". [50]
- Low socioeconomic status is also stated to be associated with increased stress, and chronic stress had been documented to impact immune function.
- A study which was undertaken by De Vries and Drent demonstrated a direct relationship between stress and sarcoidosis. [52]
- Also, the economic burden was found to be higher during the first year after the diagnosis of sarcoidosis. [53] [54]

Hanif et al. [37] made the ensuing conclusions:

- Neuro-sarcoidosis does pose a diagnostic challenge as it can simulate other neurological diseases, including CNS lymphoma and multiple sclerosis.
- Furthermore, the prognosis of neuro-sarcoidosis varies, with some patients recovering completely, while others have a chronically progressing, waxing, and waning course.
- Moreover, neuro-sarcoidosis imposes a significant economic burden upon the payer, especially in the first year following diagnosis as patients require several specialist visits to manage sarcoidosis-related comorbidities, making it a therapeutic challenge.

Conclusions

- Sarcoidosis of the urinary bladder and neuro-sarcoidosis are rare clinical entities which all clinicians through out the world should be aware in order not to misdiagnose the clinical entity.
- Both sarcoidosis of the urinary bladder and neuro-sarcoidosis pose a diagnostic challenge as they could simulate imitate other diseases.
- The prognosis of neuro-sarcoidosis varies, with some recovering completely, while others do have a chronically progressing, waxing, and waning course.
- Neuro-sarcoidosis imposes a significant economic burden upon the payer, especially in the first year ensuing the diagnosis as patients require several specialist visits to manage sarcoidosis-related comorbidities, making it a therapeutic challenge.
- Sarcoidosis may primarily afflict the urinary bladder or it may afflict organs that surround the urinary bladder and then secondary affect the urinary bladder or sarcoidosis of the spine or neuro-sarcoidosis affect the nerve supply to the urinary bladder which emanates into the development of detrusor sphincter dyssynergia.

Conflict Of Interest – Nil

Acknowledgements

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DOI:10.31579/2639-4162/247