



Sarcoidosis affecting the urinary bladder: A review of the literature

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Abstract

Sarcoidosis affecting the urinary bladder (SOUB) is rare and this could be due to direct sarcoidosis affecting the urinary bladder or due to affection of the urinary bladder secondary to spinal cord involvement. SOUB may present with non-specific lower urinary tract symptoms of urinary frequency, urgency, urge incontinence, and incomplete emptying of the urinary bladder. In cases of sarcoidosis of the spine / spinal cord affecting the urinary bladder the patient may have neurological signs in addition to lower urinary tract symptoms that tend not to be specific to sarcoidosis. Diagnosis of SOUB requires a high-index of suspicion. When there is a history of systemic or pulmonary sarcoidosis this would tend to be helpful in alerting the clinician to consider the possibility of sarcoidosis of the urinary bladder. A positive Kveim test / raised levels of serum angiotensin converting enzyme (SACE) would also help the clinician to consider the possibility of SOUB. Histopathological examination findings of non-caseating granulomas in the urinary bladder specimen or in cases of spine lesions of biopsy specimens would be indicative of SOUB or sarcoidosis of the spine affecting the urinary bladder in the absence of any other lesion in the specimen. However, sarcoidosis of urinary bladder has been reported in association with (a) malakoplakia, (b) carcinoma of the urinary bladder, (c) carcinoma of the renal pelvis. Treatment of sarcoidosis of the urinary bladder would include the use of steroid medications and at times intra-vesical instillations of steroids may be required. Other supportive treatments may be required in the management of SOUB and if associated with lesions of the spine then physiotherapy support in addition to steroid therapy and other supportive lower urinary tract symptom management approaches would be beneficial. Sarcoidosis may also regress spontaneously without treatment. Sarcoidosis of the urinary bladder, though rare, can occur and physicians need to have a high-index of suspicion for the disease in order not to miss its diagnosis.

Key Words: sarcoidosis of urinary bladder; sarcoidosis of spine; non-caseating granuloma; malakoplakia, serum angiotensin converting enzyme; Kviem test; steroid therapy; prednisolone.

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Introduction

Sarcoidosis is a disorder which tends to cause tiny nodules that are called granulomas of inflamed tissue to develop in various organs of human body.

The nodules can coalesce to form larger nodules which interfere with normal body functions such as breathing in the case of pulmonary sarcoidosis. Sarcoidosis commonly affects the lungs but it can also affect other organs as part of systemic disease or occasionally as an isolated disease involving the skin, eyes, nose, muscles, heart, liver, spleen, bowel, kidney, ureter, urinary bladder, urethra, penis, testis and epididymis, nerves, joints, spinal cord, and brain. Sarcoidosis primarily affecting the urinary bladder is extremely rare and its diagnosis would require a high index of suspicion because the symptoms tend to be non-specific and mimic symptoms of other common conditions that are encountered by general practitioners and urologists. Sarcoidosis affecting the spinal cord and the brain can also manifest with urinary tract symptoms and it's diagnosis would also require a high index of suspicion and diagnosis after

exclusion of other diseases. Because of the rarity of sarcoidosis of the urinary bladder and sarcoidosis of the spine and central nervous system. Physicians could possibly be unfamiliar with the presentation, diagnosis and management of these disease conditions. The ensuing literature review on sarcoidosis of the urinary bladder and sarcoidosis of the spinal cord and brain is divided into two parts: (A) overview and (B) Miscellaneous narrations and discussions from reported cases.

Method

Various internet data bases were searched including: Google, Google scholar, PUB Med, Educus. The search words that were used included: Sarcoidosis of urinary bladder, sarcoidosis of bladder, Sarcoid of bladder, sarcoidosis of spine, sarcoidosis of spinal cord, sarcoidosis of brain, sarcoidosis of central nervous system. 26 references were identified and used for the literature review.

Result / Literature Review

[A] Overview

Definition

Sarcoidosis is defined as a multi-system disorder of unknown cause which is characterized by the accumulation of T lymphocytes, mononuclear phagocytes, as well as non-caseating granulomas. [1] [2] [3] The lungs tend to be affected by sarcoidosis in 90% of patients who have sarcoidosis, and pulmonary sarcoidosis does account for most of the morbidity and mortality of the disease. [1] Sarcoidosis does affect many organs including the urinary bladder even though urinary bladder sarcoidosis is rare. Sarcoidosis of the urinary bladder is therefore a disorder of unknown cause that is characterized by accumulation of T lymphocytes, mononuclear phagocytes, and non-caseating granulomas.

Aetiology

The exact cause of sarcoidosis is not clearly known; nevertheless, one postulate has suggested that sarcoidosis develops when a genetically susceptible individual is exposed to specific agents in the environment and that even though the specific agents remain unknown a number of organisms that include viruses and bacteria had been suggested as agents that induce sarcoidosis. [1] Furthermore, it has been stated that non-infectious chemicals within the

environment, including beryllium, aluminium, and zirconium cause disease of the lung which simulates sarcoidosis [1]

Epidemiology

) Sarcoidosis is a global disease which affects both sexes, all races and people of all age groups [1]

) Sarcoidosis tends to be found in patients whose ages have ranged between 20 years and 40 years [1]

) It has been stated that in a minority of cases, more than one family member has been affected by sarcoidosis [1]

) Sarcoidosis occurring in children is rare. [1]

) Patients of black race are three to four times more likely to develop sarcoidosis in comparison with Caucasians and they tend to have more severe form of sarcoidosis in comparison with Caucasians [1]

Presentation

Sarcoidosis quite often causes mild symptoms which spontaneously resolve [1] Systemic sarcoidosis may affect the lungs, skin, eyes, heart, kidney, musculoskeletal system, bowel, the reproductive, system, the nervous system, the urinary bladder and other parts of the urinary tract and other organs. The presentation of sarcoidosis would depend upon the organ or organs involved by the disease.

The Nervous system

) It has been stated that sarcoidosis involvement of the nervous system occurs in about 5 percent of patients and neurological involvement by sarcoidosis may be the first sign of the disease [1]

) It has also been stated that in the late stages of the disease, meningitis, or inflammation of the membranes covering the base of the brain, sarcoidosis can cause impaired function of some structures of the brain including the pituitary gland in addition to facial weakness and paralysis.

) It has been stated that sarcoidosis may also affect the nerves in the arms and legs which result in muscle weakness, numbness, or tingling and pain [1]

) Sarcoidosis affecting the brain may also affect the urinary bladder with the development of various lower urinary tract symptoms.

) Sarcoidosis affecting the spinal cord could lead to weakness, numbness as well as gait problems for the patient.

Sarcoidosis of the urinary bladder

Isolated sarcoidosis of the urinary bladder may present with various types of non-specific lower urinary tract symptoms that may mimic other diseases. A patient who has isolated sarcoidosis of the urinary bladder may present with:

-) Urinary frequency
-) Urinary urgency
-) Nocturia
-) Incomplete emptying of the urinary bladder

If sarcoidosis of the urinary bladder causes obstruction of the ureter or ureters there may be biochemistry evidence of impairment of renal function.

The aforementioned symptoms are non-specific and would require a high index of suspicion for a diagnosis to be established. If there is a previous history of sarcoidosis this would make it easier for the clinician to consider the possibility of sarcoidosis of the urinary bladder but in the absence of a history of previous sarcoidosis the diagnosis of sarcoidosis of the urinary bladder would be made as a diagnosis of exclusion.

Clinical examination findings

In cases of isolated sarcoidosis of the urinary bladder the general and systematic examination findings could be normal despite presence of lower urinary tract symptoms. However, with regard to sarcoidosis of the spine the clinical examination findings may initially be normal, nevertheless, there may be clinical signs of neurological deficit depending upon the nerves involved by the disease but these would be non-specific to sarcoidosis.

Investigations

Microbiology

Urinalysis, urine microscopy and urine culture are routine investigations that are carried out in a patient with lower urinary tract symptoms to exclude or confirm presence or absence of urinary tract infection and if there is evidence of urinary tract infection it is treated accordingly based upon the sensitivity pattern of the organism. Urine acid fast bacterium culture could be undertaken when tuberculosis is suspected but this would not be diagnostic of sarcoidosis of the urinary bladder.

Blood tests

Haematology investigations

Full blood count and coagulation studies would constitute part of the general assessment of

patients with systemic sarcoidosis, sarcoidosis of the urinary bladder or sarcoidosis of spine but the results would not be diagnostic of sarcoidosis of urinary bladder or of the central nervous system

Routine Biochemistry investigations

Serum urea and electrolytes and liver function tests are general tests that are carried out in the general assessment of patients with systemic sarcoidosis, sarcoidosis of the urinary bladder and sarcoidosis of the spine but none of the results would be diagnostic of sarcoidosis of the urinary bladder or sarcoidosis of spine. However, evidence of impaired renal function would prompt the clinician to undertake radiological investigations that would confirm or negate presence of ureteric obstruction and hydronephrosis.

Kveim test

Kveim test may be positive in cases of sarcoidosis but would not be diagnostic of sarcoidosis of the urinary bladder or sarcoidosis of spine.

Suggested markers for sarcoidosis

A number of markers have been reported to be markers of sarcoidosis and these include: serum amyloid A (SAA), soluble interleukin-2 receptor (sIL-2R), lysozyme, angiotensin-converting enzyme (ACE), and glycoprotein KL-6 [4] [5].

It has been stated that hypercalcaemia or hypercalciuria could occur in non-caseating granulomas (NCGs) which secrete 1, 25 vitamin D and that hypercalcemia tends to be observed in 10% to 13% of patients on the other hand hypercalciuria tends to be 3 times more common. [5]

It has been intimated that elevated levels of 1, 25-dihydroxyvitamin D tend to be associated with prolonged treatment in sarcoidosis [5]. [6] Kavathia et al. [6] reported their study in which they had observed that serum 1, 25-dihydroxyvitamin D levels had been associated with patients that required repeated regimens of immunosuppressive treatment or longer than one year of treatment and that 71% of the patients whose serum 1, 25-dihydroxyvitamin D levels were greater than 51 pg/ml had required long term immunosuppressive treatment [6].

It has been stated that raised serum levels of alkaline phosphatase could suggest hepatic involvement by sarcoidosis [5] A study that was reported by Cremers et al. [7] did show that the severity of abnormalities in liver function tests is significantly linked with the degree of fibrosis and extent of the granulomatous inflammation in sarcoidosis cases.

It has been stated that angiotensin-converting enzyme (ACE) levels may be elevated in sarcoidosis and that non-caseating granulomas (NCGs) secrete ACE which could function as cytokine. [5] It has also been stated that: (a) serum ACE levels are elevated in 60% of patients with sarcoidosis at the time of diagnosis of the disease; (b) The levels of serum ACE could correlate with the total body granuloma load and the levels may be increased in fluid from broncho-alveolar lavage or in cerebrospinal fluid; (c) Sensitivity and specificity of serum angiotensin-converting enzyme (SACE) as a diagnostic test in sarcoidosis is limited in that the sensitivity is 60% and specificity is 70%; (d) SACE level is not associated with any clear prognostic value; (e) SACE levels may decline in response to treatment; (f) Decisions regarding treatment or no treatment of sarcoidosis should not be based upon SACE levels. [5]

The aforementioned markers may have a bearing on sarcoidosis; however, none of them would be considered as diagnostic of systemic sarcoidosis, sarcoidosis of the urinary bladder or sarcoidosis of the spine.

Radiological investigation

Chest X-ray

Chest X-ray is a routine test that is carried out in cases of systemic sarcoidosis and this may reveal a lesion within the lungs or hilum in cases of pulmonary sarcoidosis.

Ultrasound scan of renal tract abdomen and pelvis

Ultrasound scan of renal tract, abdomen and pelvis can be undertaken in patients who present with lower urinary tract symptoms and this may show the urinary bladder and the rest of the urinary tract. The scan would show whether or not there is a lesion within the urinary bladder or anywhere in the urinary tract including presence or absence of hydronephrosis. If there is a lesion in the renal tract, abdomen or pelvis the lesion or lesions could be biopsied under ultrasound guidance for histological examination. Ultrasound scan is a radiological imaging modality that avoids radiation which can be used in the assessment of a patient with sarcoidosis of the urinary bladder to check whether he or she is emptying his or her urinary bladder by assessing the post voiding residual urine volume within the urinary bladder and bladder scanners can be used to assess for residual urine volume at each follow-up clinic of patients with sarcoidosis affecting the bladder.

Computed tomography (CT) scan

CT scan of abdomen and pelvis would indicate presence of a lesion within the urinary bladder as well as show whether or not there is hydronephrosis as well as whether or not there is a lesion anywhere else in the abdomen and pelvis.

CT scan of thorax would show whether or not there are any lesions in the lungs, hilar regions or in the mediastinum to indicate possibility of thoracic sarcoidosis that could be biopsied.

CT scan of spine and brain would indicate whether or not there is any lesion within the spine and the central nervous system as well as the nature of the lesion.

CT scan can also be used as part of the follow-up assessment of sarcoidosis lesions found anywhere within the body. Specifically CT scan can be used in the follow-up assessment of patients with sarcoidosis of the urinary bladder or spine to see if there is relapse or absence of the sarcoidosis lesion following treatment.

Magnetic Resonance Imaging (MRI) Scan

MRI scan of abdomen and pelvis would indicate presence of a lesion within the urinary bladder as well as show whether or not there is hydronephrosis as well as whether or not there is a lesion anywhere else in the abdomen and pelvis.

MRI scan of thorax would show whether or not there are any lesions in the lungs, hilar regions or in the mediastinum to indicate possibility of thoracic sarcoidosis that could be biopsied.

MRI scan of spine and brain would indicate whether or not there is any lesion within the spine and the central nervous system as well as the nature of the lesion.

MRI scan can also be used as part of the follow-up assessment of sarcoidosis lesions found anywhere within the body. Specifically MRI scan can be used in the follow-up assessment of patients with sarcoidosis of the urinary bladder or spine to see if there is relapse or absence of the sarcoidosis lesion following treatment.

Whole body F (18)-fluorodeoxyglucose positron emission tomography (FDG-PET).

Mostard et al. [8] had reported that whole body F (18)-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning would be of additional value in the assessment of inflammatory activity in patients who have persistent symptoms in the absence of serological inflammatory activity and to detect extra-thoracic sarcoidosis lesions. Teirstein et al. [9] stated that FDG-PET scan would be

valuable in the identification of occult and reversible granulomas in sarcoidosis. However, it is important to point out that FDG-PET scan in itself would not be diagnostic of sarcoidosis per say it would only show lesions which could be targeted for biopsy for histopathological examination.

Pathology

Histology

It has been stated that the essential histological examination finding in sarcoidosis is presence of noncaseating granulomas (NCGs) associated with negative special stain findings for fungus and mycobacterium [5]

Some authors [1], [3] [10] [11] [12] [13] had stated that with regard to pulmonary sarcoidosis the initial lesion within the pulmonary system tends to be CD4+ T cell alveolitis, ensued by the development of non-caseating granulomas.

Furthermore, it had been iterated that the granulomas in sarcoidosis tend to have a tightly packed central area that is composed of macrophages, epithelioid cells, and multi-nucleated giant cells surrounded by lymphocytes, monocytes, mast cells, and fibroblasts. [14] The pathological processes in sarcoidosis elsewhere including the urinary bladder would be similar to the pathological process of pulmonary sarcoidosis.

(B) Miscellaneous narrations and discussions from reported cases

Tammela et al. [15] reported a woman who was known to have systemic sarcoidosis who subsequently developed sarcoidosis of the urinary bladder. She underwent trans-urethral resection of the urinary bladder lesion and systemic corticosteroid therapy. They stated that sarcoidosis and malakoplakia are distinct disease processes that can affect the urinary bladder. [15]

Knausz Jozsef et al. [16] reported a 63-year-old woman who had been treated for ten years because of pulmonary sarcoidosis. For a period of six months she had developed recurrent abdominal abscess and vesico-cutaneous fistula. *Escherichia coli*, was cultured from the abscess cavity and histological examination of the fistulous tract had shown features consistent with a diagnosis of malakoplakia. Pathological examination of the specimen was undertaken by using haematoxylin and eosin staining, periodic acid-Schiff, Berlin-blue, and Kossa reactions. Jozsef et al. [16] reported that

microscopic examination of the specimen had shown that the malakoplakia comprised of mainly macrophages that are known as von Hanseman cells with scattered targetoid intracytoplasmic inclusions that are referred to as Michaelis-Gutmann bodies. József et al. [16] stated that with regard to their reported patient following urological surgical intervention and antibiotic treatment the patients' symptoms and signs had resolved. József et al. [16] also stated the following:

) Malakoplakia is an acquired granulomatous disorder which was first described by Michaelis and Gutmann in 1902.

) The pathogenesis of malakoplakia is unknown; nevertheless, it is conjectured to be secondary to an acquired bactericidal defect in macrophages that occur mostly in immunosuppressed patients.

) Malakoplakia had been described in many anatomic sites, mainly in the urogenital tract.

) Malakoplakia could be complicated with the development of fistulas in different locations, vesico-coccygeal, recto-prostatic, ano-rectal fistulas had been reported in the literature, 6 cases, of malakoplakia with Boeck's sarcoidosis had been published.

Knausz Jozsef et al. [16] concluded that with regard to their reported case, the sarcoidosis and the 10-year immunosuppressive treatment with methylprednisolone might have been in the background of the development of the abdominal wall malakoplakia which was complicated by the development of vesico-cutaneous fistula; The patient had been successfully treated by means of surgical operation which was followed by antibiotic treatment.

It may be conjectural; however, it would be argued that sarcoidosis is associated with anergy and granuloma formation and that the granulomatous lesion of malakoplakia are linked by immunosuppression in patients which would perhaps explain the association of malakoplakia and sarcoidosis.

Carreiro et al. [17] reported localized amyloidosis of the bladder and sarcoidosis: analysis of a fortuitous association. This article was written in French and the paper was not available to the author.

Suzuki et al. [18] reported a 24-year-old lady who presented with a 3-month history of intermittent visible haematuria. She was found on examination to

have bilateral inguinal painless lymph-node enlargement. She had cystoscopy which showed a pedunculated papillary tumour in the urinary bladder. The results of her blood tests were normal. Histological examination of her transurethral resected urinary bladder tumour revealed a well differentiated superficial transitional cell carcinoma G1pTa. She had a computed tomography (CT) scan of thorax, abdomen and pelvis which showed bilateral pulmonary opacity as well as mediastinal and hilar lymph node enlargements. The provisional diagnosis that was made was either pulmonary metastases from carcinoma of the urinary bladder or pulmonary tuberculosis. She underwent bronchoscopy and trans-thoracic biopsy of a pulmonary nodule and histological examination of the specimen showed non caseating granulomatous inflammation with Langhan's giant cells. She had tuberculin skin test which was negative. Sarcoidosis or Sarcoid-like reaction was suspected. She also had inguinal lymph node biopsy and histological examination of the specimen was similar to the histopathological features of the pulmonary nodule. A diagnosis of carcinoma of the urinary bladder associated with systemic sarcoidosis was made. At her 15 month-follow-up she did not have any recurrence of her previous carcinoma of the urinary bladder and the pulmonary sarcoidosis had spontaneously regressed considerably without treatment. Suzuki et al. [18] stated that the association of sarcoidosis with a number of malignancies, especially lymphoma, bronchogenic carcinoma, and testicular tumour had been documented; nevertheless, at the time of publication of their paper only few reports of uro-epithelial malignancy associated with sarcoidosis had been reported and that their case was the third to be reported in the literature. Suzuki et al. [18] further stated that various speculations had existed with regard to sarcoidosis in patients who have malignant disease. Nevertheless, to date it had remained unclear whether sarcoidosis and cancer are associated or coincidental findings.

Fukutani et al. [19] 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 lymph nodes of the renal pedicle. Additionally, non-caseating granulomas had been found in the pelvic lymph nodes in a histological examination following a previous total cystectomy for carcinoma of the urinary bladder. The association of sarcoidosis with genitourinary malignancies was discussed.

French et al. [20] reported a case of malakoplakia of the urinary bladder associated with sarcoidosis in 1951.

Yukawa et al. [21] reported a 60-year-old woman who presented with skin eruptions on her forehead. For two years prior to her presentation she had been having visible haematuria and prior to her presentation she was diagnosed as having transitional cell carcinoma of the urinary bladder which was staged as TIV (T3b, N0, M0) She noticed a rash and the eventual diagnosis of the cutaneous lesion was sarcoidosis. Even though transitional cell carcinoma of the urinary bladder in this case was subsequently followed by a diagnosis of sarcoidosis of the skin, there was no obvious explanation of the two lesions developing in the same patient.

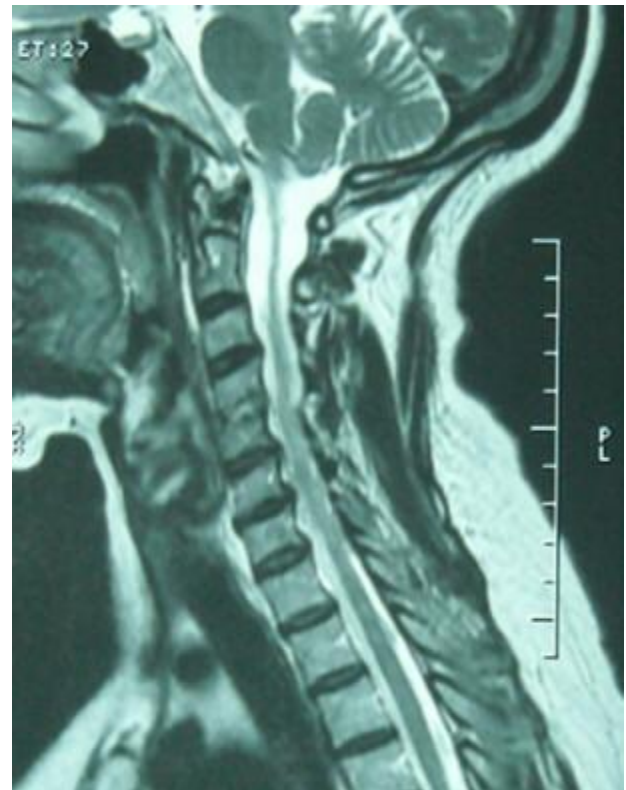


Figure 1: MRI of the spinal cord (sagittal plane), T-2 weighted image. The T9 intramedullary region (dorsal spine) of the cord was high signal intensity. Reproduced from: [22] Chouaib A, Cabanis P, Billebaud T, El Machkour M. Spinal cord sarcoidosis: An Unusual Cause of Neurogenic Bladder Dysfunction. *Journal of Neurology and Research* 2011 Jun; 1(2): 74 – 77 Short title: Spinal Cord Sarcoidosis and Neurogenic bladder doi: 10.4021/jnr21e with copy right permission granted under the Creative Commons Attribution License that allows others to share the work with an acknowledgement of the work's authorship and initial publication in the *Journal of Neurology and Research*.



Figure 2: MRI of the spinal cord (sagittal plane), T1 weighted image. The T9 intramedullary region (dorsal spine) of the cord was low signal intensity, with atrophy of cervical cord. Reproduced from: [22] Chouaib A, Cabanis P, Billebaud T, El Machkour M. Spinal cord sarcoidosis: An Unusual Cause of Neurogenic Bladder Dysfunction. Journal of Neurology and Research 2011 Jun; 1(2): 74 – 77 Short title: Spinal Cord Sarcoidosis and Neurogenic bladder doi: 10.4021/jnr21e with copy right permission granted under the Creative Commons Attribution License that allows others to share the work with an acknowledgement of the work's authorship and initial publication in the Journal of Neurology and Research.

Chouaib et al. [22] reported a 56-year-old Caucasian woman who had developed progressive weakness of both of her lower extremities which made her walking difficult which culminated in her inability to walk two months later. She gradually developed lower urinary tract symptoms including: urinary urgency, urge incontinence, nocturia with voiding more than five times per night. She was found to have spastic para-paresis, tetra-pyramidal irritation, and instability. She had computed tomography (CT) scan of spine which showed a dorsal lesion which appeared as low-signal intensity on T-1 weighting and high intensity on T-2 weighting (see figure 1), and atrophy of the cervical cord (see figure 2). She had magnetic resonance imaging (MRI) scan of the brain which was normal. Analysis of her cerebrospinal fluid showed elevated protein level, which was recorded as 0.86 mg / L. She also had serum angiotensin-converting enzyme (ACE) level test which was moderately elevated. She had a tuberculin test which was negative. She had phosphocalcic balance assessment which was initially normal but repetitive tests subsequently showed hypercalciuria (51.85 g/L) and hypophosphaturia.

She had a CT scan of the abdomen which showed a suspicious lesion in the liver. She had biopsy of the liver lesion and histological examination of the specimen showed non-caseating epithelioid granuloma. Based upon the histological examination findings it was adjudged that the findings would confirm sarcoidosis of the spinal cord. She received corticosteroid therapy which initially comprised of 500 mg per day of intravenous methyl prednisolone over 5 successive days and which was followed by taking 40 mg per day of oral prednisolone. Four weeks pursuant to commencement of the corticosteroid therapy she had MRI scan of spine which showed improvement in her spinal cord lesion. She gradually continued to improve and her urinary symptoms also improved as a result of which the dose of her oral prednisolone was tapered down by 10 mg weekly down to a daily maintenance dose of 10 mg. She had been walking with two sticks at the time of the report of her case. One month after she had been commenced on corticosteroid therapy she had urodynamic test which showed decreased urinary bladder volume at first desire to void at 80 ml, bladder capacity of 230 ml, and marked detrusor hyperreflexia (see figure 3). The urodynamic test did not show any evidence of uninhibited sphincter relaxation or detrusor- sphincter dyssynergia. The corticosteroid steroid therapy continued to improve her symptoms but she did not have a repeat urodynamic assessment.

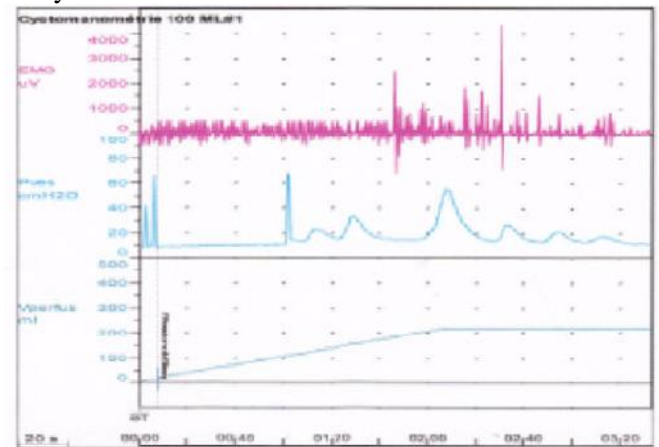


Figure 3: EMG cystometry, involuntary detrusor contraction. Reproduced from: [22] Chouaib A, Cabanis P, Billebaud T, El Machkour M. Spinal cord sarcoidosis: An Unusual Cause of Neurogenic Bladder Dysfunction. Journal of Neurology and Research 2011 Jun; 1(2): 74 – 77 Short title: Spinal Cord Sarcoidosis and Neurogenic bladder doi: 10.4021/jnr21e with copy right permission granted under the Creative Commons Attribution License that allows others to share the work with an acknowledgement of the work's authorship and initial publication in the Journal of Neurology and Research.

Fitzpatrick et al. [23] in 1996 reported the first case of neurogenic urinary bladder dysfunction which was associated with neuro-sarcoidosis. Fitzpatrick et al. [23] reported that the urodynamic findings of the patient did show detrusor hyperreflexia with detrusor-sphincter dyssynergia which correlated with the patient's magnetic resonance imaging (MRI) examination which had shown intramedullary involvement at the mid-thoracic level.

Sakaibara et al. [24] reported a 30-year-old man who slowly developed progressive gait of ataxia of vestibular origin, deafness, and hallucination which had developed into versive seizure and stupor. He had computed tomography (CT) scan and magnetic resonance imaging (MRI) scan of the brain which showed an anteromedial frontal lobe lesion associated with mild ventricular enlargement. He had examination of his cerebrospinal fluid which showed pleocytosis and with raised total protein and angiotensin-converting enzyme levels. He had endoscopic biopsy of a lung lesion and histological examination of the specimen showed epithelioid granuloma. He initially received prednisolone 60 mg per day orally which resulted in improvement of his symptoms. However, after the dose of his steroid therapy was tapered, he developed urinary urgency, urge incontinence, urinary frequency and relapse of his gait ataxia. He had urodynamic assessment which did show detrusor hyperreflexia. Further treatment with prednisolone improved his urinary symptoms as well as his neurological symptoms. Sakaibara et al. [24] stated that the anteromedial frontal lobe lesion seemed to have been responsible to the voiding disturbances in their patient with neuro-sarcoidosis.

Sakaibara et al. [25] reported a 42-year-old woman who slowly developed progressive spastic gait, numbness of her left hand, urinary frequency and urgency as well as voiding difficulty which had worsened gradually over one year. She did undergo C2 to C7 laminoplasty for relief of a C2 to C6 cervical disc herniation where there was mild swelling of the cervical cord. Her gait only improved transiently for a period of two weeks only. Two months subsequently, she was not able to walk without the use of a walking aid. She had magnetic resonance imaging (MRI) scan of the spine which showed a swelling of the spinal cord at the level of C2 to C7. She also developed bilateral lymph node enlargement, ocular uveitis, and an increased concentration of serum angiotensin-converting enzyme (ACE). She had endoscopic lymph node

biopsy and pathological examination of the specimen showed non-caseating epithelioid granuloma. Based upon the clinical findings and the histopathology findings of the biopsy specimen a diagnosis of sarcoidosis of the spinal cord was made. She received pulse steroid treatment of 1000 mg per day of intravenous methyl prednisolone for the initial 3 successive days which was followed by 60 mg per day of oral prednisolone with benefit. The dose of her steroid treatment was tapered to 40 mg on alternate daily basis and she was referred to another hospital 4 months later. At that time her difficulty gait had relapsed together with urge urinary incontinence and difficulty with micturition. She was also constipated. Clinically on admission she was found to have spastic tetra-paresis which was prominent in her legs. Her clinical examination also showed brisk deep tendon reflexes and positive Babinski's signs; decreased sensation to pin prick bilaterally below the C6 dermatome. The results of her routine blood tests were within normal range. Analysis of her cerebrospinal fluid showed normal cell count but a slight increase in the protein content of 42 mg / dl. The angiotensin-converting enzyme level was normal within her serum and in her cerebro-spinal fluid. She had magnetic resonance imaging (MRI) scan of her spine which showed a swelling at the level of C2 to C7 of the spinal cord and this appeared as low-signal on T-1 weighted imaging and high intensity on T-2 weighted images. There was evidence of contrast enhancement within the C4/5 intramedullary region that had extended longitudinally through the surface of the spinal cord. She received 3 further courses of pulse steroid treatment starting with 40 mg per day of oral prednisolone and 200 mg per day of cyclosporine which improved her neurological symptoms. She nevertheless, subsequently started having symptomatic attacks which included: a sudden onset of severe, throbbing headache, twice per week, which was followed by conjunctival congestion, flushing of face, lacrimation, nasal congestion, without presence of skeletal muscle spasms or bowel contraction. Her attacks were associated with hypertension with a blood pressure of 190/100 mm Hg without any increase in her heart rate. She had CT scan of brain which was normal and she was given 5 mg of sub-lingual nifedipine which resulted in resolution of her symptoms. She was also catheterized which relieved her voiding symptoms. She had urodynamic assessment which revealed the ensuing results: Her first desire to void was recorded at 350 ml (normal range 100 ml – 300 ml), and the maximum cystometric capacity was 670 ml (normal range 200 ml to 600 ml) which was suggestive of

impairment of urinary bladder sensation. There was evidence of detrusor hyperreflexia during the end of the filling phase of the cystometry. During the voiding phase of the cystometry there was no evidence of detrusor-sphincter dyssynergia, the detrusor pressure at maximum flow in relation to the flow rate based upon the Abrams-Griffiths normogram indicated equivocal obstruction and normal detrusor pressure based upon Schäfer's normogram and the results were adjudged to be indicative of neurogenic bladder. She was taught intermittent self-catheterization and commenced on 2 mg per day of prazosin, a selective alpha1 antagonist which improved her symptoms. Lessons learnt from this case report would confirm that even though sarcoidosis in a number of cases may not directly involve the urinary bladder sarcoidosis involving the spinal cord and the central nervous system may affect the urinary bladder leading to lower urinary tract symptoms including, urinary frequency, urgency, urge incontinence and voiding difficulties including incomplete emptying of the urinary bladder that may require use of intermittent self-urinary bladder catheterization as well as selective alpha1 antagonist and that even though steroid therapy may lead to improvement in voiding symptoms related to the development of neurogenic bladder may persist.

Kim et al. [26] in 2001 reported a patient with neuro-sarcoidosis who initially presented with urinary frequency that was secondary to neurogenic bladder dysfunction.

Cuervo Pinna et al. [27] in 2001 reported a 65-year-old man who developed sarcoidosis of the lung pursuant to having had intra-vesical instillations of mitomycin C for superficial urothelial carcinoma of the urinary bladder. Cuervo Pinna et al. [27] stated that 2 previous cases had been reported of the development of lung toxicity after intra-vesical instillation of Mitomycin C. Cuervo Pinna et al. [27] further stated that there had never been any previous report of sarcoidosis of the lung developing after intra-vesical instillation of mitomycin C. Whilst the aetiology of sarcoidosis may not be clearly understood it may be argued that the inflammatory reaction to the mitomycin C treatment may have been responsible for the development of the lung sarcoidosis. On the other hand it could also be argued that the development of sarcoidosis of the lung was coincidental and not related to the mitomycin treatment.

Conclusion

Sarcoidosis of the urinary bladder, though rare, can occur and physicians need to have a high-index of suspicion for the disease in order not to miss its diagnosis.

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