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Genitourinary Sarcoidosis: A Single Institution Experience and Review of the Literature

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ABSTRACT

INTRODUCTION: Sarcoidosis is a multisystemic disorder characterized by granulomata in the diseased tissue. Genitourinary (GU) involvement is rare. The authors report 3 patients in whom GU sarcoidosis was the initial presentation without any systemic manifestation.

METHODS: The Medical University of South Carolina database of patients with sarcoidosis between the years 1986 and 2007 was reviewed to identify individuals with GU sarcoidosis. PubMed was searched for other reported cases.

RESULTS: The university database included 934 patients; 3 patients had GU sarcoidosis. All were African-American males, ranging in age from 27-48 years old. All initial laboratory results were normal. Case 1 presented with a painless left epididymal mass and no history of urinary tract infection. Scrotal ultrasound (US) revealed a hypoechoic left testicular lesion and an epididymal mass. Two months later, a repeat US showed bilateral testicular hypervascular epididymal masses. A left radical orchiectomy was performed. Pathology showed granulomatous orchitis. The patient later developed a large right epididymal mass and subcutaneous nodule. Angiotensin converting enzyme (ACE) and lactate dehydrogenase (LDH) were elevated, consistent with sarcoidosis, and CXR showed mediastinal lymphadenopathy. Case 2 presented with painless testicular lumps and no constitutional symptoms. Eventually, CXR showed bilateral hilar adenopathy. Endoscopic bronchial biopsy confirmed the diagnosis. He had atrophic testes with firm left posterior epididymis, and US showed multiple bilateral small hypoechoic lesions. The testicular mass did not respond to steroid therapy and excisional biopsy of the mass, which revealed granulomatous orchitis. Case 3 presented with prostatic nodules. Transrectal US and biopsy showed sarcoidosis. He subsequently developed hypogonadism and inguinal lymphadenopathy. Lymph node biopsy revealed noncaseating granuloma consistent with sarcoidosis. He also developed neurosarcoidosis and bilateral lymphadenopathy.

DISCUSSION: In the authors' institution, GU sarcoidosis was found only in 0.03% of all patients with sarcoidosis. GU involvement is now reported in 72 cases in the literature, but these are the first known cases to be reported with GU manifestation as the initial presentation of sarcoidosis. Sarcoidosis should be considered as a part of the workup and differential diagnosis in patients with GU granulomas.

KEYWORDS: Genitourinary sarcoidosis; Sarcoidosis; Testicular granuloma

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Abbreviations and Acronyms

ACE = angiotensin converting enzyme
AFP = alpha fetoprotein
GU = genitourinary
HCG= human chorionic gonadotropin
MUSC = Medical University Of South Carolina
US = ultrasound

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INTRODUCTION

Sarcoidosis is a multisystemic disorder, characterized histologically by the presence of noncaseating epithelioid cell granulomas in affected organs. Sarcoidosis is most commonly diagnosed in the lungs and mediastinal lymph nodes [1]. Genitourinary (GU) involvement is extremely rare [2] and occurs in only 0.2% of all clinically diagnosed patients [3]. The organs affected, in order of frequency, include the epididymis, testis, and prostate [4]. Due to its low incidence, GU sarcoidosis can easily be misdiagnosed. Three cases of GU sarcoidosis were identified in a comprehensive sarcoidosis database. The following sections describe the incidence, location, and presentation of GU sarcoidosis in these 3 cases, and provide a review of the relevant literature.

METHODS

After obtaining institutional review board approval, the sarcoidosis database for the years 1986-2007 (inclusive) of the Medical University of South Carolina (MUSC) was searched to identify patients with GU involvement. In addition, a PubMed (US National Library of Medicine and National Institutes of Health) literature search was performed to identify any reported cases of GU, testicular, epididymal, or prostate sarcoidosis between January 2003 and December 2008.

RESULTS

The MUSC sarcoidosis database included 933 patients over the 9-year period. Of these, only 3 patients had GU sarcoidosis. Each of these patients presented with GU involvement in the absence of other systemic manifestations. Results of the literature review are presented in the discussion.

Figure 1a. Transverse Scrotal Ultrasound for Case 1, Demonstrating Multifocal Hypoechoic Lesions (arrows).
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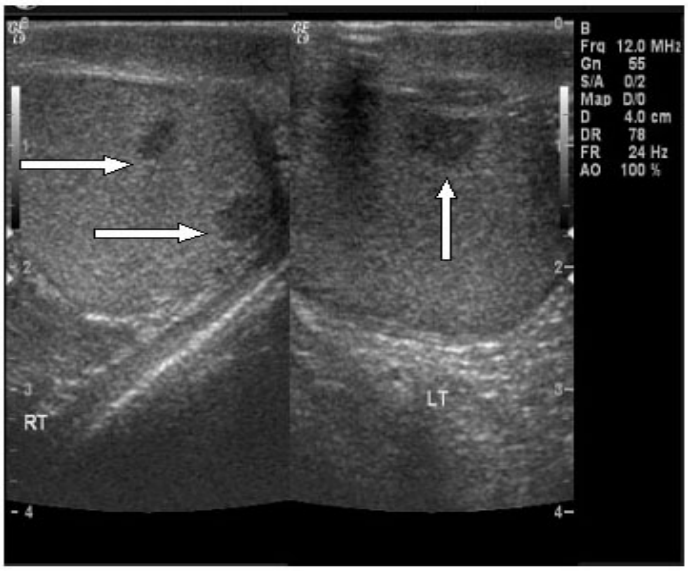

Case 1

The initial case was a 31-year-old African-American male who presented with a painless left epididymal mass in the absence of urinary tract infection or sexually transmitted disease. Scrotal ultrasound (US) revealed a 4 mm hypoechoic left testicular lesion (Figure 1a) and an enlarged left epididymal mass. All laboratory results were negative, including urinalysis, alpha fetoprotein (AFP), human chorionic gonadotropin (HCG),

Figure 1b. Testicular Histology in Low and High Power for Case 1, Demonstrating Multifocal Granulomatous Orchitis (arrows). doi: 10.3834/uij.1944-5784.2010.04.01f1b

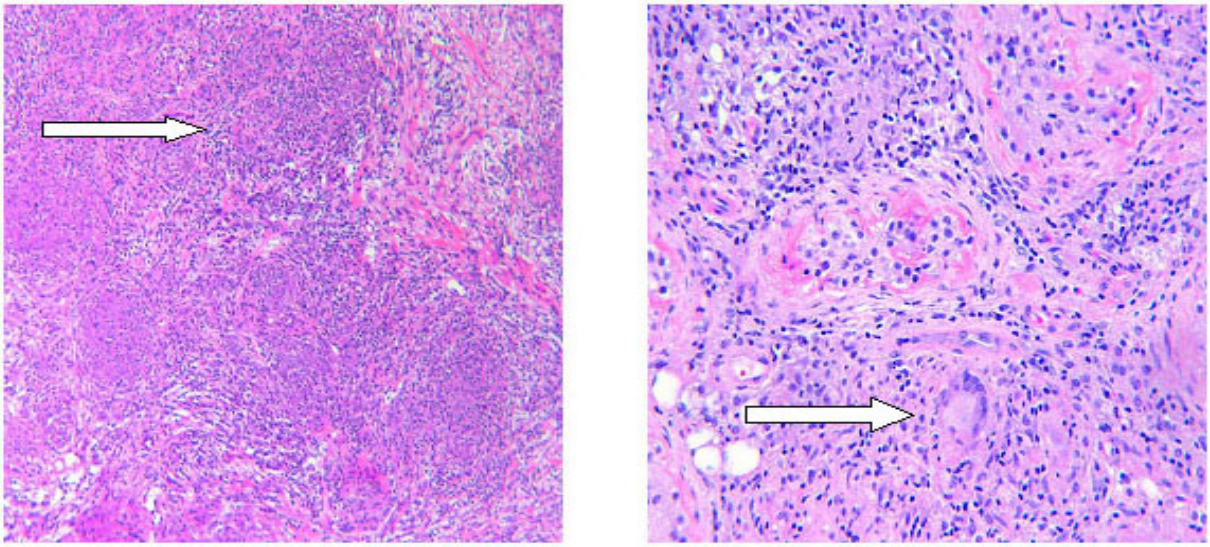

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Figure 1c. Chest Radiograph for Case 1, Demonstrating Pretracheal Lymphadenopathy (arrow) and Parenchymal Nodular Disease Suggestive of Sarcoidosis.
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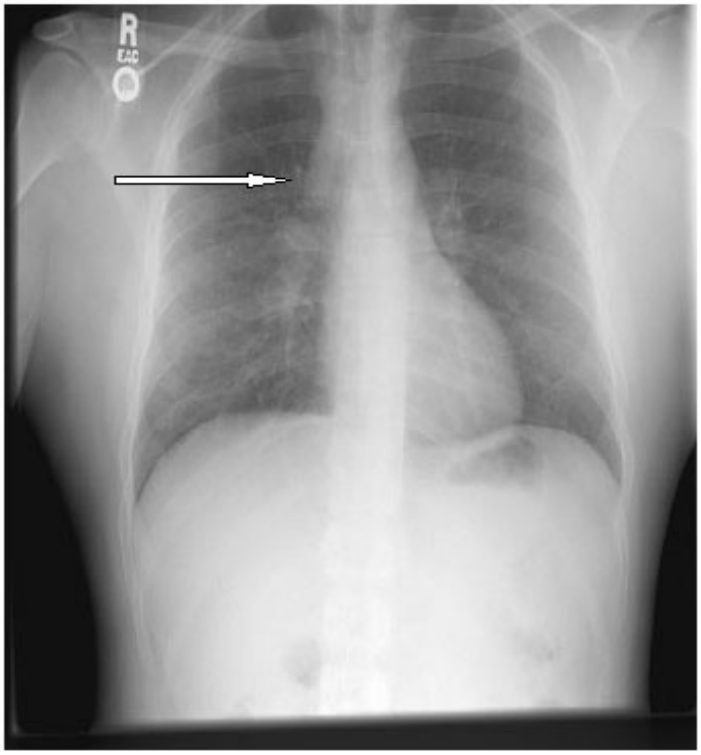


protein purified derivative (PPD), and urinary acid-fast bacilli (AFB). A chest radiograph and renal US were unremarkable. The patient returned 2 months later with a large left hemiscrotal mass with a confluent testis and epididymis and a larger right epididymal mass. Repeated US showed bilateral testicular masses with bilateral heterogeneous epididymal enlargement with hypervascularity. Given the rapid enlargement of the masses and complete involvement of the left testis, a left radical orchiectomy through an inguinal approach was performed. The preoperative chest radiograph was normal. Frozen section showed granulomatous orchitis. During the follow-up period (4 months) the patient's right testis and epididymis coalesced to form a large mass, and he developed subcutaneous nodules. Given the previous pathology of granulomatous orchitis (Figure 1b), serum angiotensin converting enzyme (ACE) and lactate dehydrogenase (LDH) were checked. The results of both measures were elevated, consistent with sarcoidosis. The patient progressed to hypogonadism as evidenced by his low serum testosterone, erectile dysfunction, and lethargy. A repeat chest radiograph (Figure 1c) revealed pretracheal and perihilar lymphadenopathy with parenchymal nodular disease. Corticosteroid therapy with 20 mg of hydrocortisone (tapered to 10 mg), and androgen supplementation were initiated. However, the patient's symptoms worsened, and methotrexate was started at 15 mg weekly. The patient also began prednisone 15 mg daily until he reported improvement of respiratory symptoms. Methotrexate was tapered and discontinued because of elevated liver enzymes at 6 months, and prednisone was tapered to 5 mg with remission for another year. The follow-up period was 4 years. The patient also received testosterone replacement secondary to his hypogonadism.

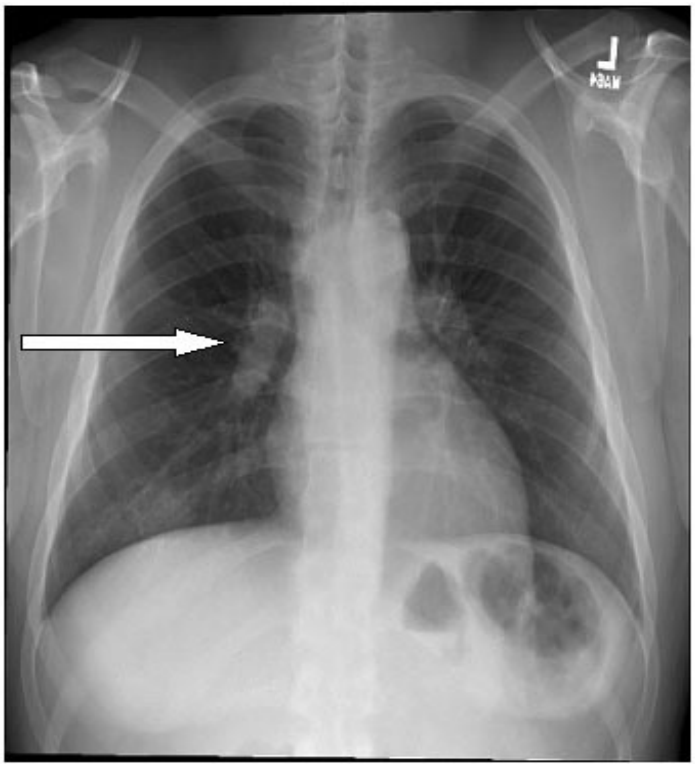
Case 2

Case 2 was a 27-year-old African-American male who initially presented with painless testicular nodules. He also complained of an occasional productive cough, which began just shortly after presentation with the testicular nodules in the absence of other constitutional symptoms. His examination was remarkable for slightly atrophic testes with some firmness in his left posterior epididymis. There were no clearly palpable intratesticular masses, but the patient noticed irregularity of the surface of the testis. A scrotal US showed multiple bilateral small hypoechoic lesions. The serum AFP and HCG were negative. A chest radiograph (Figure 2a) showed bilateral hilar, right paratracheal, and subcarinal adenopathy, consistent with sarcoidosis. The diagnosis was confirmed with transbronchial needle biopsy under US guidance. The patient began corticosteroid therapy at 15 mg prednisone daily; however, there was no decrease in size of the testicular nodules. Testicular exploration was performed through an inguinal approach, and testicular biopsy was done under US guidance (Figure 2b). Analysis of frozen sections confirmed the diagnosis of granulomatous orchitis. The predisone was ultimately tapered to 5 mg daily for one year, and the patient remained in remission for another year with no prednisone. The follow-up period was 2 years. He continues to be clinically stable.

Case 3

Case 3 was a 49-year-old African-American male who presented with an abnormal digital rectal examination with a firm, nodular prostate. He had a transrectal US and biopsy which revealed granulomatous prostatitis. There were no symptoms present. He subsequently developed inguinal lymphadenopathy. A lymph node biopsy revealed noncaseating granuloma consistent with sarcoidosis. A chest radiograph demonstrated hilar lymphadenopathy, confirming the diagnosis of sarcoidosis. He later developed neurosarcoidosis with parenchymal brain masses seen on magnetic resonance imaging (MRI) scans of the brain. He was initially placed on 60 mg of prednisone, which was tapered gradually to a maintenance dose of 10 mg to 20

Figure 2a. Chest Radiograph for Case 2, Demonstrating Perihilar Lymphadenopathy (arrow).
doi: 10.3834/uij.1944-5784.2010.04.01f2a



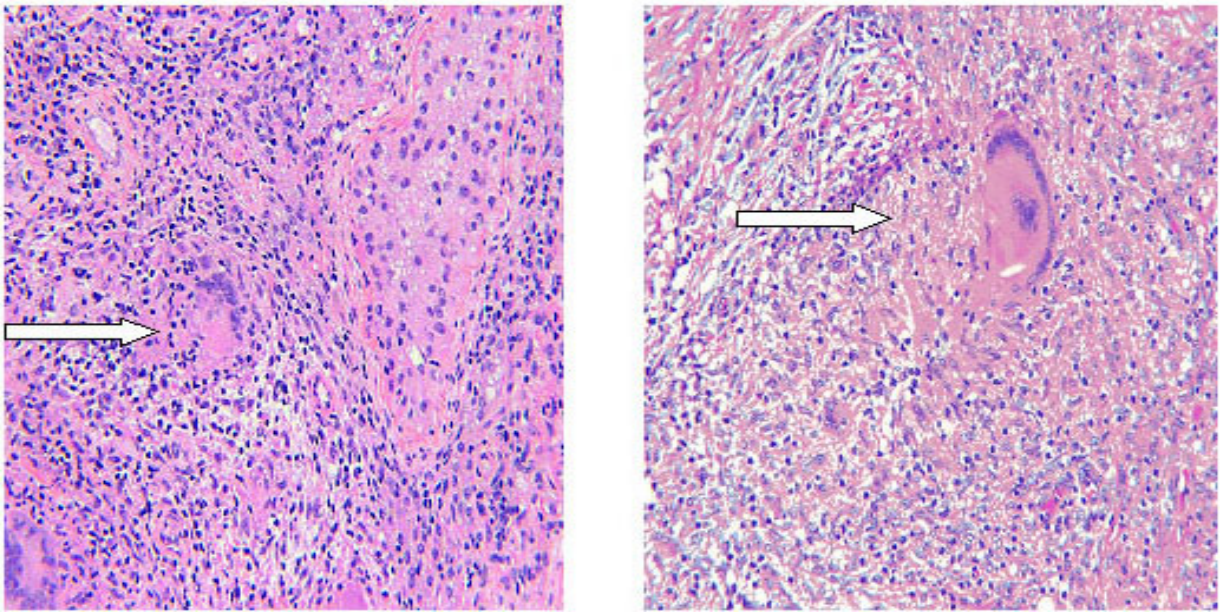
mg after 6 months. The therapy for this patient was tailored based on his neurologic symptoms; medications were alternated among high doses of prednisone, cyclophosphamide, and infliximab (Remicade; Centocor Ortho Biotech Inc, Horsham, PA, USA) over 28 months. Once his symptoms had stabilized, he was maintained on 5 mg of prednisone every other day with no further progression of disease. The total follow-up period was over 12 years.

DISCUSSION

Sarcoidosis is a multisystem disease of unknown etiology characterized by noncaseating granuloma formation in the affected organs. The disease onset occurs most commonly in individuals between the age of 20 and 40 years. In 84% of the cases, the disease involves the lungs [1]. Sarcoidosis is typically detected as an abnormality on a chest radiograph. Characteristic radiographic abnormalities include bilateral hilar lymphadenopathy and/or reticulonodular parenchymal infiltrates.

Genitourinary involvement is extremely rare [2] and is reported to occur in less than 0.2% of reported cases, with increased incidence in African-American men [3,5]. Kodama et al [6] found 60 cases reported in the literature since 1949. The present authors identified another 9 cases reported thereafter in a PubMed search between January 2003 and December 2008. This brings the total number of reported cases to 72.

Figure 2b. Excisional Biopsy for Case 2, Demonstrating Granulomatous Orchitis (arrows).
doi: 10.3834/uij.1944-5784.2010.04.01f2b



Epididymal involvement is most common, followed by testicular involvement [6-8]. Epididymal involvement is typically unilateral but may occur bilaterally. Testicular involvement is reported in less than 1% of cases of epididymal sarcoidosis [9-15]. All 3 of the patients identified by the present authors presented with GU sarcoidosis on the basis of genitourinary signs or symptoms; there were no other symptomatic systemic manifestations of sarcoidosis. However, each patient subsequently developed other clinical sequelae of the disease. Case 1 and Case 2 are the first known reported cases presenting initially with epididymal and testicular involvement.

Only 4 previous patients were reported to have prostate sarcoidosis [16-19]. However, in all 4 cases, prostate involvement was not the first clinical manifestation of the disease. Schauman [16] reported the first case of prostatic sarcoidosis in a patient with disseminated disease in 1936. There were 2 subsequent cases reported as part of the systemic disorder [17,18]. Furusato and colleagues [19] diagnosed incidental prostate sarcoidosis in a prostate biopsy in a patient with systemic sarcoidosis. Case 3 from the authors' database is the fifth patient reported with sarcoidosis of the prostate; however, Case 3 is the first reported to present with prostate involvement as the initial manifestation of sarcoidosis. As with the other patients reported with prostate sarcoidosis, he developed systemic manifestations of the disease in the form of neurosarcoidosis.

Scrotal sonographic characteristics of sarcoidosis usually show hypoechoic masses affecting the testes and epididymis. These lesions are difficult to differentiate from malignant masses [11]; therefore, malignancy should be considered in these cases. In the absence of bilateral lesions, negative tumor markers, and systemic manifestation of sarcoidosis, malignancy needs to be definitively assessed and biopsy should be done [20].

Therapy for GU sarcoidosis is controversial. Many patients with sarcoidosis show spontaneous total remission over a period of up to 3 years. Corticosteroid therapy will typically be instituted if the function of a vital organ is affected or if hypercalcemia is present [21]. In GU sarcoidosis, corticosteroid therapy should be considered in patients with unilateral testicular involvement or bilateral testicular involvement after malignancy has been excluded [2]. Cases 1, 2, and 3 were initiated on 20 mg prednisone with a subsequent steroid taper to a maintenance dose of 10 mg daily. Failure of corticosteroid therapy to control the symptoms or stop progression of the symptoms is a potential indication for surgical intervention [22], as in Case 2. For surgical treatment, 2 approaches have been adopted. A more radical approach, suggested by Singer et al [23], is to perform a radical orchiectomy. This is problematic with bilateral involvement because the result is a patient who is infertile and has hypogonadism from a nonmalignant condition. This occurred in Case 1, who was placed on testosterone replacement due to his agonadal state. This approach was used due to diffuse involvement and rapid growth of the mass in this patient, which was worrisome for malignancy. Such an approach should be reserved for symptomatic patients who are not responding to medication or for patients with diffuse involvement suggestive of malignancy. An alternative, more conservative approach includes inguinal exploration and intraoperative US-directed excisional biopsy [24], with frozen section examination to exclude malignancy. This approach was adopted in Case 2 to confirm the diagnosis while performing testis-sparing surgery. Such an approach is more reasonable, especially for patients with a single testis or who have bilateral involvement of the testes. Orchiectomy in this approach should be reserved for diffuse involvement of the testis or malignancy in the biopsy [3,23].

CONCLUSIONS

GU sarcoidosis is extremely rare. Including the 3 cases in the MUSC database, only 72 cases have been reported through December 2008. Prostate involvement is exceedingly rare. GU sarcoidosis should be considered in the presence of noncaseating granulomas of the GU tract. An elevated serum ACE, hypercalcemia, or hypercalciuria as well as the presence of systemic manifestations of sarcoidosis may facilitate the diagnosis of GU involvement. Corticosteroid therapy should be considered in symptomatic patients. Surgery may be required in some patients who do not respond to steroids, or in cases suspicious for malignancy. Cognizance of this clinical entity can potentially allow earlier systemic therapy in patients likely to develop progressive disease.

REFERENCES

[1] Roos N, Bick U, Vassallo P, et al. Thoracic sarcoidosis [in German]. *Radiologe*. 1990;30(12):581-590.

[2] Ryan DM, Lesser BA, Crumley LA et al. Epididymal sarcoidosis. *J Urol*. 1993;149(1):134-136.

[3] Turk CO, Schacht M, Ross L. Diagnosis and management of testicular sarcoidosis. *J Urol.* 1986;135(2):380-381.

[4] Gross AJ, Heinzer H, Loy V, Dieckmann KP. Unusual differential diagnosis of testis tumor: intrascrotal sarcoidosis. *J Urol.* 1992;147(4):1112-1114.

[5] Mayock RL, Bertrand P, Morrison CE, Scott JH. Manifestations of sarcoidosis. Analysis of 145 patients, with a review of nine series selected from the literature. *Am J Med*. 1963;35:67-89.

[6] Kodama K, Hasegawa T, Egawa M, Tomosugi N, Mukai A, Namiki M. Bilateral epididymal sarcoidosis presenting without radiographic evidence of intrathoracic lesion: Review of sarcoidosis involving the male reproductive tract. *Int J Urol.* 2004;11(5):345-348.

[7] Ritchie AW, Hindmarsh JR. Bilateral epididymal sarcoid. Br *J Urol*. 1983;55(2):240-241.

[8] Hausfeld KF. Primary sarcoidosis of the scrotum: case report. *J Urol.* 1961;86:269-272.

[9] Schaeffer J, Nussbaum M, Meyersfield S. Paratesticular mass as a presenting sign of sarcoidosis. *Pediatrics.* 1980;66(3):462-463.

[10] Haas GP, Badalament R, Wonnell DM, Miles BJ. Testicular sarcoidosis: case report and review of the literature. *J Urol.* 1986;135(6):1254-1256.

[11] Rehman J, Rizkala ER, Chughtai B, Khan SA. Hypoechoic testicular mass: a case of testicular and epididymal sarcoidosis. *Urology*. 2005;66(3):657.

[12] Wong JA, Grantmyre J. Sarcoid of the testis. *Can J Urol.* 2006;13(4):3201-3203.

[13] Hurd DS, Olsen T. Cutaneous sarcoidosis presenting as a testicular mass. *Cutis*. 2000;66(6):435-438.

[14] Revington PJ. Testicular sarcoidosis. *Br J Urol*. 1994;73(5):596-597.

[15] Massarweh NN, Bhalani VK, Shaw KK, Crawford B, Lang E, Davis R. Testicular presentation of sarcoidosis and organ preservation: case report and review of management strategies. *Urology*. 2006;67(1):200.

[16] Schaumann J. Lymphogranulomatosis benigna in the light of prolonged clinical observations and autopsy findings. *Br J Derm Syph*. 1936;48:399-446.

[17] Morris SB, Gordon EM, Corbishley CM. Prostatic sarcoidosis. Review of genitourinary sarcoidosis. *Br J Urol.* 1993;72(4):462-464.

[18] Todd RF 3rd, Garnick M. Prostatic adenocarcinoma, sarcoidosis and hypercalcemia: an unusual association. *J Urol.* 1980;123(1):133-134.

[19] Furusato B, Koff S, McLeod DG, Sesterhenn IA. Sarcoidosis of the prostate. *J Clin Pathol.* 2007;60(3):325-326.

[20] Khan SA, Richenberg JL, Fletcher MS. Scrotal swelling in sarcoidosis. *J R Soc Med*. 2004;97(10):487-488.

[21] Winnacker JL, Becker KL, Katz S, Matthews MJ. Recurrent epididymitis in sarcoidosis. Report of a patient treated with corticosteroids. *Ann Intern Med*. 1967;66(4):743-748.

[22] McWilliams WA, Abramowitz L, Tiamson EM. Epididymal sarcoidosis: case report and review. *J Urol*. 1983;130(6):1201-1203.

[23] Singer AJ, Gavrell GJ, Leidich RB, Quinn AD. Genitourinary involvement of systemic sarcoidosis confined to testicle. *Urology.* 1990;35(5):442-444.

[24] Strawbridge LR, Blute ML, James EM, Gillespie. Intraoperative ultrasonographically guided biopsy in testicular sarcoidosis: a case report. *J Urol*. 1990;143(6):1229-1231.