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Disseminated Sarcoidosis With Testicular Involvement: A Case Report and Literature Review

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Abstract: Sarcoidosis is a multisystem inflammatory disease of unknown etiology that predominantly affects the lungs and intrathoracic lymph nodes. Testicular sarcoidosis is a rare presentation of this disease. We review the case of a patient with stage 2 sarcoidosis with bilateral intrascrotal involvement along with classic pulmonary, lymphoid, and dermatological manifestations. We provide a literature review of testicular sarcoidosis and discuss the diagnostic challenges and the management of intrascrotal mass in setting of disseminated sarcoidosis.

Key Words: sarcoidosis, scrotal mass, testicular sarcoidosis, intrascrotal sarcoidosis, sarcoidosis of the genitourinary tract, lupus pernio, ichthyosis, ichthyosiform sarcoidosis

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Sarcoidosis is a multisystem inflammatory disease of unknown etiology that predominantly affects the pulmonary system. Although the most common presentation involves granulomatous changes of the lungs and intrathoracic lymph nodes, sarcoidosis can involve almost any organ. Testicular sarcoidosis is a rare manifestation of this disease.

CASE REPORT

A 46-year-old male from the West Indies with a past medical history significant for Graves disease status-post radioactive ablation and chronic normocytic anemia presented to the emergency room with a chief complaint of testicular discomfort and swelling of 1-year duration. He reported increasing bilateral testicular swelling over the past year and recently had become associated with pain and discomfort. He denied any hematuria, dysuria, urinary discharge, or urinary hesitancy. He reported progressive dyspnea on exertion and a nonproductive cough for the prior 10 months. However, he denied hemoptysis, orthopnea, or paroxysmal nocturnal dyspnea. He noted 30 to 40 pounds of unintentional weight loss over the past year and the presence of nonhealing skin lesions over his right face of >10 months duration. He denied recurrent fevers, chills, or night sweats. His social history was pertinent for heterosexual intercourse with commercial sex workers. He also had a history of inhalational cocaine use 1 year before presentation but denied any tobacco use.

At initial presentation, he was afebrile. Heart rate was 115 beats per minute, blood pressure was 124/73 mm Hg, respiratory rate was 16 breaths per minute, and oxygen saturation was 96% on room air.

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He appeared well-nourished and was not in respiratory distress. Chest auscultation revealed bilateral inspiratory crackles and expiratory wheezes. He was tachycardic with normal heart sounds. Pertinent negative findings included the absence of jugular venous distension, organomegaly, or lower extremity edema. Genitourinary examination revealed bilateral testicular fullness with mild tenderness to palpation. Also noted were multiple, raised, irregular papules on the right side of the face, the largest measuring 1.0 cm by 1.5 cm, and bilateral polygonal scaly plaques over the pretibial areas of the lower extremities that had been present since adolescence (Fig. 1).

Laboratory studies revealed normocytic anemia (hemoglobin 11.6 g/dL, MCV 90 fL) with eosinophilia (8.4%) and monocytosis (18.0%). His white blood cell count was within normal range at 4000 cells/mL. His serum calcium level was normal at 9.2 mg/dL. Scrotal ultrasound showed multiple, confluent hypoechoic masses within both testicles (Fig. 2). Chest radiography showed bilateral interstitial infiltrates predominately over the lower lobes and bilateral hilar fullness (Fig. 3). A thoracic computed tomography (CT) showed marked lymphadenopathy involving the mediastinum, bilateral hilar, subcarinal, and right paratracheal region, along with fine nodularity and thickening of interstitial markings in the bilateral lung parenchyma (Figs. 4A, B). The nodules seen on CT were distributed in a perilymphatic distribution, especially along the fissural surfaces and the peribronchovascular axial interstitium. In addition, a CT of the abdomen showed extensive abdominal and pelvic lymphadenopathy. The patient was ruled out for active pulmonary tuberculosis. He was found to have an elevated lactate dehydrogenase level of 258 U/L (reference range, 98 to 192 U/L), an elevated angiotensin-1 converting enzyme level of 193 U/L (reference range, 9 to 67 U/L), and an elevated serum CD4/CD8 ratio of 9.5 (CD4 count of 540 cells/mL and a CD8 count of 57 cells/mL). Tumor markers for testicular tumors were unremarkable: serum α -fetoprotein was 4 ng/mL (reference range, 0 to 20 ng/mL) and total β HCG was <2 mIU/mL (reference range, <5 mIU/mL). Serologies for HIV and fungal diseases including histoplasmosis, cryptococcosis, and coccidiomycosis were all negative.

In light of the systemic lymphadenopathy, bilateral intrascrotal masses, facial skin lesions, lower extremity plaques, and thoracic radiographic findings, a formal tissue diagnosis was sought. The patient underwent a fiberoptic bronchoscopy identifying friable, irregular infiltrated mucosa of the tracheobronchial tree, whitish plaques in trachea, and a near complete occlusion of the right middle lobe (Fig. 5A). An endobronchial biopsy of a right middle lobe segment revealed squamous metaplasia with evidence of epitheloid non-caseating granulomas (NCGs) (Fig. 5B); the biopsy was negative for dysplasia or malignancy. Baseline pulmonary function tests had earlier revealed a mixed restrictive and obstructive ventilatory defect. The significant obstructive component was attributed to the significant endobronchial involvement of the granuloma as demonstrated during fiberoptic bronchoscopy. He also underwent a shave biopsy of the largest nonhealing skin lesion over his right facial cheek that revealed dermatitis with NCGs (Fig. 5C). As testicular malignancy needed to be excluded in this young male patient with intrascrotal masses, testicular biopsies using the inguinal route of both the right and left testicles were performed. The testicular biopsies displayed multinucleated giant cells within epitheloid NCGs without evidence of dysplasia or malignancy (Fig. 5D). With histologic evidence of NCGs from the 3 involved sites, along with the clinical and radiologic presentation, we diagnosed the patient with disseminated stage 2 sarcoidosis with extrapulmonary involvement of the testicles and skin (facial lesions representing lupus



FIGURE 1. Hyperpigmented, scaly plaques spread diffusely across the bilateral lower extremities representing an ichthyosiform sarcoidosis.

pernio and ichthyosis of the lower extremities). He was started on corticosteroids (prednisone 1 mg/kg orally), as well as β 2-agonist metered-dose inhaler and trimethoprim/sulfamethoxazole prophylaxis while immunosuppressed on prednisone. His testicular discomfort and dyspnea significantly improved with the initiation of above treatments, and he was discharged home with close follow-up to monitor symptoms and for titration of steroids.

DISCUSSION

Sarcoidosis is a multisystem inflammatory disease that can present with a diverse array of clinical manifestations. The disease resolves spontaneously in most individuals, whereas significant impairment occurs in about 15% to 20% of patients.¹ Around 90% of patients demonstrate pulmonary involvement appearing as adenopathy and or parenchymal infiltration that can progress to advanced pulmonary fibrosis.¹ The most common extrapulmonary manifestations involve the lymphoid, ophthalmologic, and dermatologic systems. Clinically significant involvement of spleen, liver, bone, heart, kidney, or central nervous system occurs in 2% to 6% of patients.²

Although skin lesions are seen in 20% to 35% of patients with sarcoidosis, the scaly plaques of ichthyosis, as noted in this patient, are rarely observed.³ Ichthyosiform lesions are hyperpigmented, polygonal scales that present in variable sizes and thickness.^{4,5} Biopsy specimens of these scales often show NCGs and hyperkeratosis. Ichthyosiform sarcoidosis is a marker for systemic disease with 95% of reported cases demonstrating multisystem involvement.⁶ Scrotal lesions in the setting of such cutaneous manifestations should raise the suspicion for testicular sarcoidosis. Lupus pernio, also observed in our patient, is a red-to-purple nodular or plaque-like indurated lesion that primarily involves the cheeks, nose, lips, ears, or periorcular regions.^{5,7} Lupus pernio is the most specific cutaneous finding of sarcoidosis with biopsy showing granulomatous inflammation. Similar to ichthyosiform sarcoidosis, lupus pernio can be seen in patients with testicular sarcoidosis because this lesion is associated with extensive systemic disease.

Involvement of the genitourinary tract, as illustrated in our case report, is a rare phenomenon. Clinically diagnosed genitourinary sarcoidosis in men is reported to be <0.2% of cases and 5% of autopsy studies.⁸ Within the genitourinary system, sarcoid granulomas are more frequently seen within the epididymis, testis, and prostate, while rarely affecting the penis, spermatic cord, or the scrotum itself.⁹ Sarcoidosis of the male reproductive system can present as a painless intrascrotal mass with swelling or can masquerade as an acute epididymo-orchitis. Testicular and epididymal involvement in sarcoidosis is usually unilateral.¹⁰ Bilateral testicular lesions as demonstrated in our case are less prevalent. The commonest reproductive structure involved is the epididymis, implicated in 75% of genital sarcoidosis, followed by the testes, seen in 50% of cases. Although our patient's testicular biopsy supported the diagnosis of sarcoidosis, it is unclear whether there was involvement of either epididymis as these areas were not biopsied.

Ethnicity plays an important role not only in the development of sarcoidosis but also in the disease severity and progression. Epidemiological studies in the United States have shown that African Americans have a significantly higher age-adjusted incidence for sarcoidosis compared with white Americans: 34 versus 11 cases per 100,000 persons.¹¹ The vast majority of patients are young adults between the ages of 20 to 40 years. African American patients tend to have more chronic

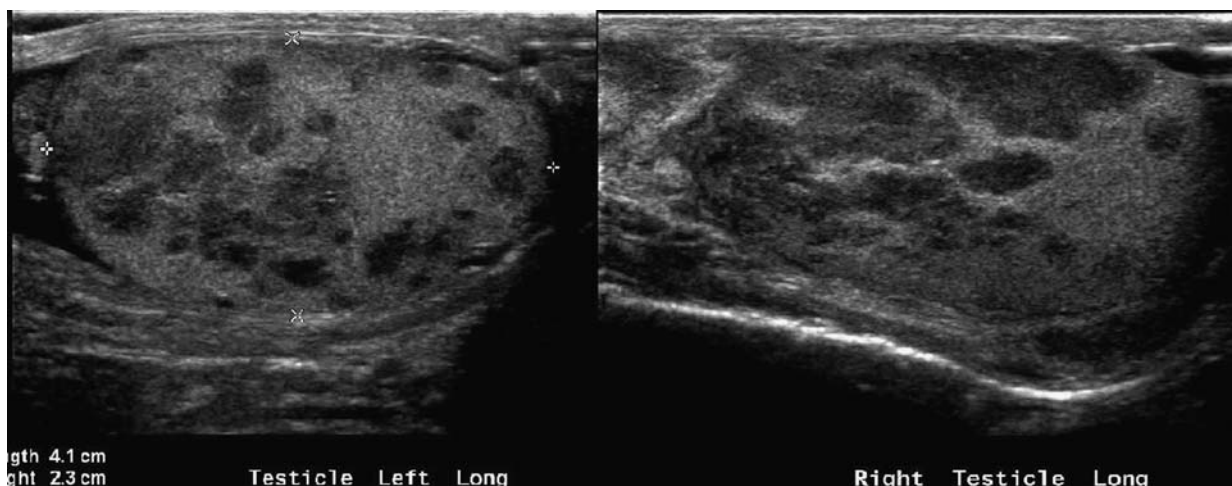


FIGURE 2. Scrotal ultrasonography showing multiple, hypochoic lesions within both testicles.



FIGURE 3. Frontal chest radiograph shows bilateral hilar fullness and perihilar micronodular opacities.

progressive disease, worse long-term prognosis, and higher rates of relapse. They also have an increased incidence of extrathoracic sarcoidosis, including lupus pernio and involvement of the reproductive system. Genitourinary sarcoidosis occurs 10 times more frequently in this population (Table 1).^{5,12,13}

On ultrasound imaging, testicular sarcoidosis appears as hypo-echoic lesions that can mimic testicular neoplasms.¹⁴ MRI and gallium-67 scintigraphy have been used to establish testicular involvement of sarcoidosis.^{15,16} These lesions exhibit low signal intensity on T2-weighted images and enhancement on contrast-enhanced T1-weighted images.¹⁷ However, these modalities are nonspecific. A more definitive approach is testicular biopsy and findings of NCGs within the reproductive tract in the clinical context of sarcoidosis after other diagnoses have been excluded.

When confronted with scrotal lesions as seen in our case, the differential diagnosis includes malignancy (germ cell tumors or lymphoma), infection (tuberculosis, histoplasmosis,

coccidioidomycosis, or lymphogranuloma inguinale), inflammatory disease (sarcoidosis, berylliosis, or sperm granulomas), or benign anatomic entities such as cysts (Table 2). Testicular sarcoidosis usually presents between the ages of 20 to 40 years overlaps with the peak incidence of testicular malignancies. Given that testicular neoplasms are predominantly diagnosed in this age cohort, malignancy should still remain high in the differential diagnosis of testicular lesions.

Optimal management and treatment of suspected testicular sarcoidosis remains a source of debate. When there is bilateral testicular involvement, negative testicular tumor markers, and other sites of systemic sarcoidosis, some have argued for biopsy followed by observation as spontaneous resolution of testicular sarcoidosis can occur. However, sarcoidosis may be independently associated with a higher incidence of testicular cancer. Leatham et al¹⁸ in a retrospective review of 1120 patients with germ cell testicular tumors over a 13-year period found 9 patients with a combined diagnosis of sarcoidosis and testicular tumor. In another study, Jeurkar et al¹⁹ observed that the incidence of granulomatous disease among patients with testicular germ cell tumor represented a 10-fold increase compared with the general population. Both these studies suggesting a link between testicular cancer and sarcoidosis are retrospective. There are no studies which have prospectively followed patients with testicular sarcoidosis to confirm a predisposition for testicular cancer.

The potential downside of an observation schema is permitting an undiagnosed testicular malignancy to grow and metastasize. Corticosteroid therapy for sarcoidosis can unwittingly provide false reassurance by diminishing the inflammation surrounding testicular tumors.^{20,21}

Another consideration when differentiating between testicular cancer and testicular sarcoidosis is what to make of mediastinal adenopathy. Mediastinal and hilar adenopathy are observed in both sarcoidosis and testicular cancers. Furthermore, benign noncaseating granulomatous hilar or mediastinal lesions can be observed with seminomas, teratomas, teratocarcinomas, and embryonal carcinomas.^{21–23} These sarcoid-like reactions presumably develop in response to soluble tumor antigens or are derived from T-cell-mediated reactions to tumor cells.²¹ Sarcoid-like reactions do not seem to affect cancer prognosis. In one study of testicular cancer patients with sarcoidosis, 80% of patients had spontaneous resolution of granulomatous disease without affecting the cancer prognosis.²⁴ Although these sarcoid-like areas do not always represent neoplastic recurrence, they should not

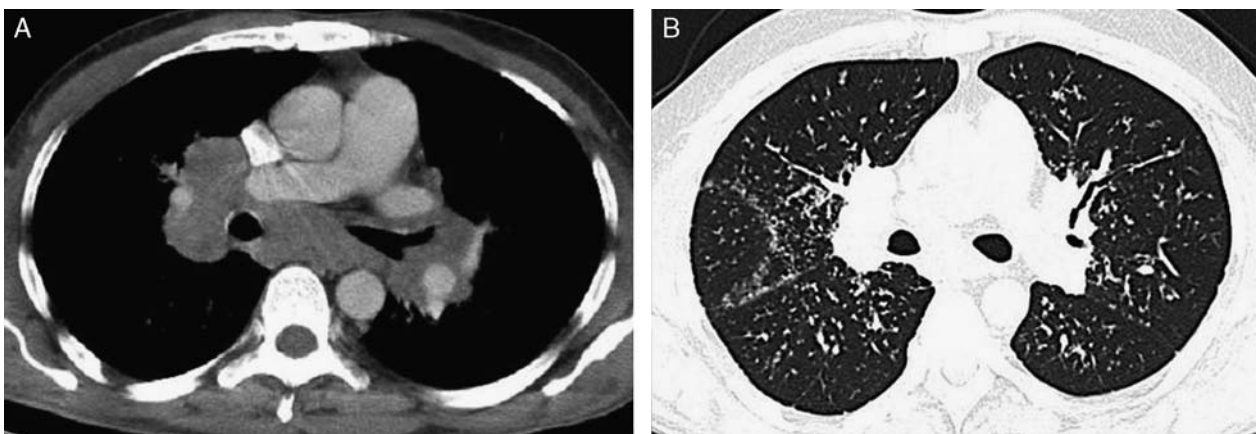


FIGURE 4. Axial thoracic computed tomography showing extensive hilar and mediastinal lymphadenopathy (A) and extensive pulmonary micronodules with a perilymphatic distribution (B).

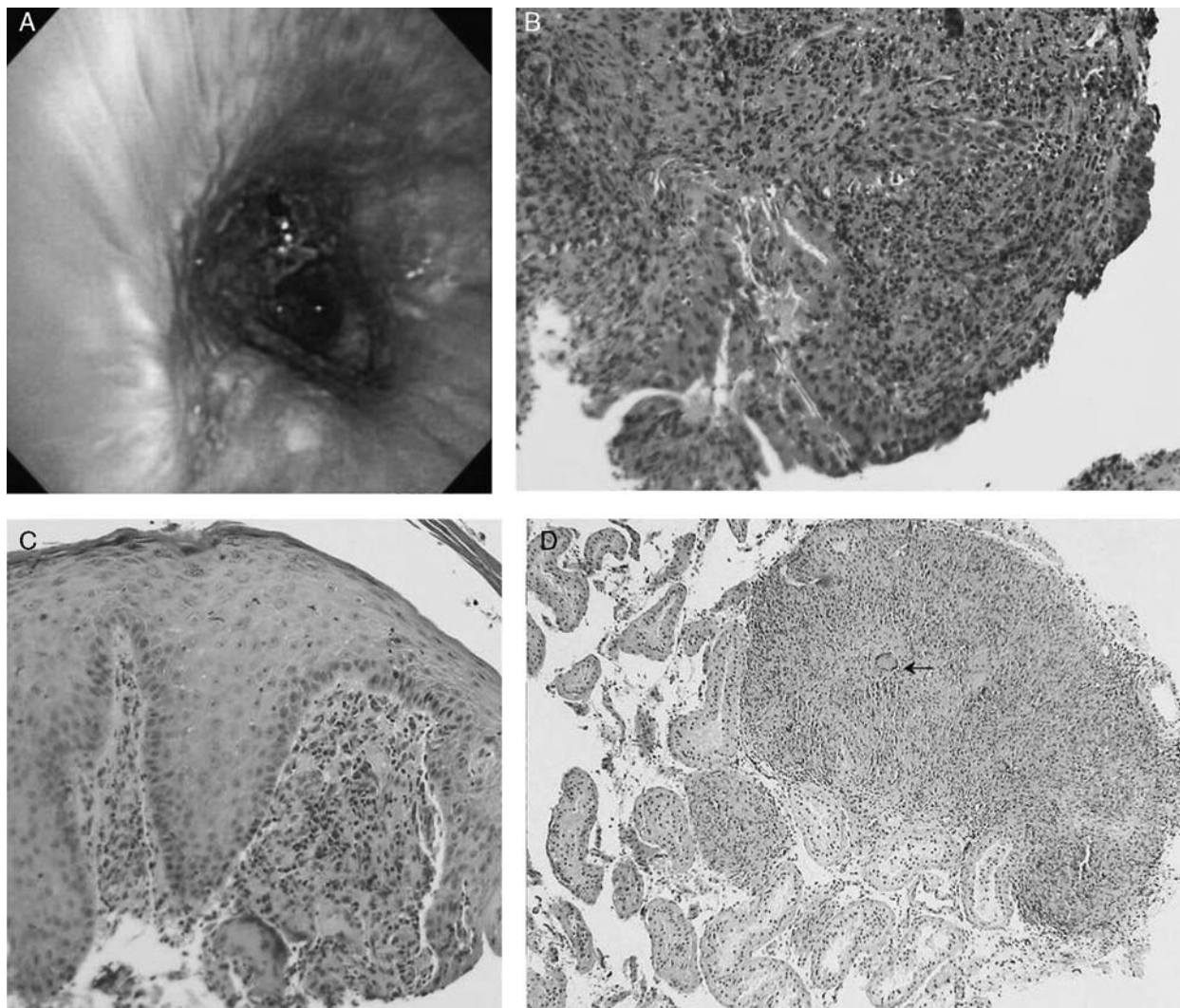


FIGURE 5. A, Image obtained using flexible bronchoscope showing friable, irregular, infiltrated tracheobronchial mucosa. B, Photomicrograph of the endobronchial biopsy specimen demonstrating multinucleated giant cells within noncaseating granulomas. C, Photomicrograph of the skin shave biopsy of the largest right facial lesion showing dermatitis with noncaseating granulomas. D, Photomicrograph of the testicular biopsy specimen featuring normal seminiferous tubules at left with a multinucleated giant cell (black arrow) among the epithelioid granulomas.

preclude the pursuit of establishing tissue diagnosis to rule out malignancy with metastasis.

Serum markers are not always helpful in excluding testicular cancer. α -fetoprotein can be elevated in cases of sarcoidosis with hepatic involvement. Approximately 10% of patients with sarcoidosis have hepatic involvement, a finding that is more common in African American patients.²⁵ Lactate

dehydrogenase can also be elevated in sarcoidosis—as in our patient—and has limited sensitivity and specificity for detecting relapse of testicular germ cell tumors (Table 3).²⁶

Surgical management of suspected testicular sarcoidosis with radical orchiectomy is favored by some authors in light of the above considerations and because of the significant disease

TABLE 1. Few Characteristics of Genitourinary Sarcoidosis

Rare phenomenon, <0.2% of sarcoidosis cases
Predominantly involves epididymis (75% of cases) and testis (50% of cases) and usually is unilateral
Rarely affects spermatic cord, penis, or scrotum
Higher incidence and severity in African Americans (10 times more frequent)
Usually presents between the ages of 20–40 years

TABLE 2. Differential Diagnosis of Testicular Lesions in Patients With Sarcoidosis

Malignancy (germ cell tumors or lymphoma)
Infection (tuberculosis, histoplasmosis, coccidioidomycosis, or lymphogranuloma inguinale)
Inflammatory disease (sarcoidosis, berylliosis, or sperm granulomas)
Torsion
Hematoma
Cysts

TABLE 3. Considerations When Differentiating Between Testicular Cancer and Testicular Sarcoidosis: A Diagnostic Challenge

Sarcoidosis is independently associated with higher incidence of testicular cancer
Usual presentation of testicular sarcoidosis between ages of 20 to 40 years overlaps with peak incidence of testicular malignancies
Sarcoidosis hilar lymphadenopathy can also be a sign of testicular tumor metastasis
Noncaseating granulomatous hilar lesions can be observed in testicular cancer
α -fetoprotein and lactate dehydrogenase can be elevated in testicular sarcoidosis and neoplasm
All patients could initially seem to respond to steroids and immunosuppressive therapy

burden that granulomatous inflammation can place on the functionality of the affected testicle. However, a more conservative testicular preservation approach with inguinal exploration and intraoperative ultrasound-guided biopsy may avoid unnecessary orchiectomies.^{18,27} The management approach should be on a case-by-case basis in view of a patient's clinical and objective findings. Morbidity associated with testicular sarcoidosis includes oligospermia and infertility which are thought to be secondary to the fibrosis and occlusion of the ductus epididymis.^{8,28} Treatment with corticosteroids has been shown in some cases to restore spermatogenesis.²⁸

CONCLUSIONS

Although sarcoidosis of the male reproductive system is uncommon, it should be considered in the differential diagnosis of testicular lesions in the appropriate clinical setting. Once testicular sarcoidosis is suspected, it should not preclude pursuit of a malignancy workup including tissue biopsy of testicular lesions. An aggressive diagnostic approach is indicated in testicular sarcoidosis. These patients require close follow-up and monitoring even when a testicular biopsy is negative for malignancy.

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