

Urologic and Urinary Manifestations of Sarcoidosis

Julien Vanderhulst*

Department of Internal Medicine, Centre Hospitalier Universitaire (CHU) Brugmann, Brussels, Belgium

*Corresponding author: Julien Vanderhulst, Department of Internal Medicine, CHU Brugmann – site Brien, Rue du Foyer Schaerbeekois 36, 1030 Brussels, Belgium, Tel: 3224779370; E-mail: Julien.VANDERHULST@chu-brugmann.be

Received date: September 06, 2017; Accepted date: September 13, 2017; Published date: September 20, 2017

Copyright: © 2017 Vanderhulst J. This is an open-access article distributed under the terms of the creative commons attribution license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Sarcoidosis is a chronic granulomatous disease that most commonly affects the lungs, but concomitant -or exceptionally isolated- extrapulmonary involvement is frequent. Urologic symptoms may occur in a patient known with sarcoidosis or may reveal the disease.

The present review illustrates the protean nature of the disease, which can manifest with any of the common urologic symptoms and can be mistaken for other conditions such as infection and cancer. An insight into diagnostic and therapeutic management is also proposed.

We hope to increase awareness about urologic manifestations of sarcoidosis in order to help the clinicians avoiding misdiagnosis, which could expose the patients to unnecessary medications or surgical procedures, progressive disease, recurrence and long-term sequelae.

Keywords: Urologic sarcoidosis; Genitourinary sarcoidosis; Extrapulmonary sarcoidosis; Nephrocalcinosis; Kidney stone; Sarcoid pseudotumour

Abbreviations ACE: Angiotensin-Converting Enzyme; ADH: Antidiuretic Hormone; Beta-HCG: Beta-Human Chorionic Gonadotropin; LDH: Lactate Dehydrogenase; FDG-PET scan: Fluorodeoxyglucose-Positron Emission Tomography Scan.

Introduction

Sarcoidosis is a chronic systemic disorder caused by the formation of noncaseating granulomas in affected organs. Although the aetiology is unknown, sarcoidosis is characterized by T-cell and macrophage activation, leading to Th1-type immune response. The hypothesis of environmental agents acting as triggers on a genetic background is supported by many experimental and epidemiologic findings [1]. The disease affects both men and women and most of the patients are adults less than 40 years of age. Women and African-Americans are more likely to be affected.

While lung, lymph nodes and liver are frequently involved, extrapulmonary sarcoidosis accounts for half of the patients with thoracic disease. Extrapulmonary sarcoidosis without lung involvement is rare (about 2% of patients with sarcoidosis).

Urinary and urologic sarcoidosis is a very infrequent disease (less than 1% of patients with sarcoidosis). It can present as part of a multisystem disease or as an isolated finding. Subclinical granulomatous involvement is probably more frequent, and sarcoidosis is often a more disseminated disease that what is perceived from the clinical history only, as suggested by post-mortem studies on patients with sarcoidosis [2].

The diagnosis relies on three criteria: a clinical and radiological picture consistent with the diagnosis of sarcoidosis, the demonstration

of noncaseating granulomas and exclusion of other granulomatous diseases. However, for extrapulmonary disease, granulomatous involvement of a single organ is considered not sufficient to affirm the diagnosis [1]. The finding of concomitant sarcoidosis in another organ or previous pulmonary sarcoidosis supports the diagnosis.

Urinary and Urologic Sarcoidosis

The urologic manifestations of sarcoidosis can be divided schematically into three groups on the basis of the underlying pathophysiologic mechanism: direct (“primary”) urologic granulomatous involvement, indirect (“secondary”) granulomatous involvement (neurological or endocrine sarcoidosis), and indirect nongranulomatous involvement (through sarcoidosis-induced changes in calcium metabolism).

Primary urologic sarcoidosis

Although the epidemiology of sarcoidosis is difficult to study because of variability in the definition, clinical presentation and diagnostic tests [1], kidney and epididymis appear the most frequent affected organs of the urologic tract [3].

Kidney: Silent renal granulomatous involvement is frequent (as much as 20%) [4], and may become clinically significant when the number and extent of granulomas is sufficient to cause impairment in renal function. Renal disease is more frequently related to calcium deposit as mentioned later. The most typical form of renal sarcoidosis is called granulomatous interstitial nephritis (GIN), which represents an inflammatory process in the renal interstitium that can lead to declining renal function and tubular dysfunction, sometimes with progressive fibrotic changes in the renal interstitium leading to long-term sequelae. The urinalysis of patients with GIN often shows a bland sediment, but sterile pyuria or mild proteinuria can also be seen. Glomerular disease is less frequent than GIN, but IgA nephropathy has been described in patients with sarcoidosis. Rarely, renal sarcoidosis

can present with a renal mass sometimes referred to as “sarcoid pseudotumour” [5]. In this case, the clinical and radiological picture of renal sarcoidosis can mimic either a cancer, a lymphoma or an infectious process like tuberculosis. The diagnosis can therefore be challenging, especially in the case of isolated renal disease. On the other side, cases of renal carcinomas have been reported in patients with otherwise known sarcoidosis [6].

Epididymis: Involvement of the epididymis can also mimic a neoplastic process, as it often presents as a unilateral, palpable mass which may be painful or not. Azoospermia has been described in the setting of epididymal sarcoidosis [7].

Testis: Testes are one of the most frequently affected organ in urologic sarcoidosis. More than three quarter of the cases also display concomitant pulmonary sarcoidosis, [8] even though testicular sarcoidosis as a presenting feature of the condition has also been described [9]. Unilateral or bilateral involvement can occur, and adjacent structures such as epididymis and spermatic cord are often affected. Scrotal swelling, nodules and painless solid mass are the most common presenting features.

Because of the concern of malignancy, about one third of the patients with testicular sarcoidosis undergo (unnecessary) orchiectomy [10]. However, distinction between sarcoidosis and cancer may be challenging because coexistence of testicular cancer and sarcoidosis has been described, and some data point to an increased risk of cancer in patients with sarcoidosis [11]. Furthermore, sarcoid-like reaction may develop in response to certain tumors, which may complicate the accurate histological diagnosis [12]. Of note, elevated LDH levels have been found in some cases of sarcoidosis and therefore are also not considered reliable [13,14]. Elevation of other tumour markers such as alpha-foetoprotein and beta-HCG has been less frequently reported [15].

Due to these considerations, some authors advise radical orchiectomy in all patients with unilateral testicular masses, whereas other prefers a more conservative approach [16]. In selected cases, frozen section assessment could be a way to decrease the number of unnecessary orchiectomies [17].

Prostate: Several cases of post-mortem incidental findings of prostatic sarcoidosis have been reported in patients with otherwise widespread disease [3] while other patients exhibit clinical signs and symptoms directly related to prostatic involvement and some cases are discovered in the diagnostic workup for PSA elevation. About 15 cases of prostatic sarcoidosis have been published [18]. The peripheral part of the gland is affected preferentially, which may suggest that prostatic sarcoidosis can be paucisymptomatic and thus underdiagnosed.

Bladder: Sarcoidosis can directly involve the urinary bladder and cause nonspecific urinary symptoms like hematuria, urgency, frequency and dysuria. Because of histological similarities, malakoplakia has been related to sarcoidosis by some authors [19,20].

Penis and scrotum: Sarcoidosis of the penis and scrotum represents a cutaneous form of the disease. Typical lesions appear on the penile shaft or glans as waxy or erythematous papules or nodules [21]. The urethral meatus can be affected, and ulcerations or mass like lesions have been reported [22]. Again, possible carcinoma remains a concern for the differential diagnosis.

Urethra: While this form of sarcoidosis is unlikely to be asymptomatic because of anatomic considerations, the urethral localization of sarcoidosis has been very rarely described in the

medical literature. [23,24]. Both cases occurred in women. It can present with chronic obstructive and irritative voiding symptoms.

Ureters: Ureteral sarcoidosis is uncommon with only a few cases in the literature [25-28]. It can present with renal colic, microscopic or macroscopic hematuria and hydronephrosis. Sarcoid retroperitoneal lymphadenopathy or fibrosis may also cause obstructive uropathy [29,30].

Secondary urologic sarcoidosis

As a systemic disease, sarcoidosis can also manifest with urologic symptoms in the absence of direct involvement of the urologic tract or adjacent structures.

Bladder dysfunction: Involvement of the nervous system is quite common in patients with sarcoidosis. Lower urologic complaints and progressive symptoms such as frequency may be the presenting features of the disease when spinal cord is involved [31-33]. Most of these patients however would have associated neurologic symptoms such as weakness, dysarthria, facial numbness or seizures.

Endocrine manifestations: The hypothalamus is the most frequently involved endocrine gland in sarcoidosis. Primary pituitary involvement occurs less frequently. Granulomatous infiltration of the hypothalamo-hypophyseal region leads to tertiary or secondary endocrine dysfunction, and can manifest as central hypogonadism [34,35]. Actually, almost half of the patients with sarcoidosis have been found to have low circulating free testosterone level, which seems not to be related to usual symptoms of hypogonadism such as diminished muscle function, exercise intolerance or depressed mood. Absence of appropriate increase of gonadotrophin levels argue for a global dysfunction of the hypothalamo-pituitary-gonadal axis in these patients [36]. Patients with hypothalamic involvement can also present with polyuria and polydipsia due to dysregulation of thirst (primary polydipsia) or ADH (diabetes insipidus) [37].

Vitamin-D and calcium metabolism

Disordered calcium metabolism is actually the main cause of renal disease in patients with sarcoidosis. The *primum movens*-also described in other granulomatous diseases-is increased extrarenal 1-alpha-hydroxylase activity and production by activated mononuclear cells within granulomas, lymph nodes and lungs. Unlike what is seen under physiologic conditions, the 1-alpha-hydroxylase activity in sarcoidosis is only substrate-dependent with no feedback inhibition. This leads to increased conversion of 25-hydroxyvitamin D to calcitriol and hence marked hyperabsorption of dietary calcium [38]. Calcitriol-induced resorptive bone disease and renal tubular calcium reabsorption also contribute to calcium metabolism dysregulation. As a consequence, hypercalcemia is a well-known complication of systemic sarcoidosis and is seen in about 10% of patients. The increased calcium load is excreted in the urine and hypercalciuria is three times more common than hypercalcemia [39]. This is of particular importance regarding urologic complications of sarcoidosis, since hypercalcemia and hypercalciuria both contribute to significant renal disease.

Nephrolithiasis: Nephrolithiasis occurs in about 10% of patients with sarcoidosis [4] and renal colic may be the first sign of sarcoidosis in about 4% of patients [40]. As a result, evidence of renal colic due to calcium-containing kidney stone (usually calcium oxalate), particularly

in a patient without known risk factors for nephrolithiasis, should prompt the urologist to search for other manifestations of sarcoidosis.

Nephrocalcinosis: Nephrocalcinosis is seen in about 5% of patients with sarcoidosis. Unrecognized and untreated chronic hypercalcemia and hypercalciuria lead to tubulointerstitial inflammation and calcium deposits with ensuing progressive kidney disease. Most patients would present with elevated creatinine and unremarkable urinalysis. In fact, nephrocalcinosis has been diagnosed in more than 50% of cases amongst patients with sarcoidosis-related renal insufficiency [4]. While most patients with nephrocalcinosis are asymptomatic, some exhibit tubulointerstitial dysfunction with nephrogenic diabetes insipidus. Early detection and treatment of hypercalcemia and hypercalciuria is warranted to avoid fibrotic change and irreversible renal damage [41].

Diagnosis

The diagnosis of urologic and urinary sarcoidosis is challenging because the clinical and radiological manifestations are nonspecific and sarcoidosis may mimic many other conditions such as cancer or infection. Virtually any urologic or urinary symptom could be related to sarcoid involvement of the urologic tract. As previously mentioned, the diagnosis requires a compatible clinical and radiological picture, demonstration of noncaseating granulomas and exclusion of other granulomatous diseases. In this case of extrapulmonary involvement, demonstration of concomitant sarcoidosis in another organ or previous pulmonary sarcoidosis strongly supports the diagnosis.

Whenever possible, a biopsy of the involved organ should be obtained. Careful histologic analysis with cultures and stains is warranted because other granulomatous disease like tuberculosis, other mycobacterium infections, fungal infections, syphilis, filariasis, schistosomiasis, drug-induced granulomatosis, vasculitis (granulomatosis with polyangiitis), Crohn disease, brucellosis, histoplasmosis, lymphoma and paraneoplastic sarcoid-like reaction may all involve the genito-urinary tract and mimic sarcoidosis.

All patients suspected with urologic sarcoidosis should have chest imaging, pulmonary function tests, serum chemistry, urine analysis, electrocardiogram, ophthalmologic examination and tuberculin skin test [1]. Because of the high prevalence and the long-term damaging effect of hypercalciuria, we recommend an assessment of 24-hour calciuria in all patients.

Distinguishing sarcoid pseudotumour from primary renal or testicular malignancy may be particularly difficult because neither conventional imaging nor FDG-PET scan are discriminant. Moreover, patients may experience constitutional symptoms such as fatigue, malaise, anorexia, fever and weight loss in both conditions [1]. Local or mediastinal sarcoid lymphadenopathy may mimic a metastatic disease. Serum markers such as beta-HCG and alpha-foetoprotein may help in case of testicular mass but are not 100% reliable as previously mentioned. Serum ACE is often measured in sarcoidosis and can be found elevated in 60% of the patients [42]. Nevertheless, its use as a diagnostic tool is controversial because of its lack of sensitivity and specificity. For example, elevation of ACE has been reported in metastatic testicular seminoma [43].

However, from an epidemiologic point a view, a renal or testicular mass is more likely to be a primary neoplasm than a sarcoid pseudotumour. In order to avoid misdiagnosis, pre- or intraoperative biopsy should be considered in doubtful cases (i.e. in patients with

otherwise known or suspected sarcoidosis) for organ preservation purpose.

Treatment

Due to its rarity, there are no available clinical trials on the therapeutic management of sarcoidosis of the urologic tract, which is therefore mostly derived from the experience in pulmonary sarcoidosis. As in the case of pulmonary localization, the treatment is tailored to the extent and severity of the disease.

Most cases follow a benign and self-limited course and some patients experience spontaneous resolution. Thus watchful waiting may be an option in paucisymptomatic cases. When the disease is symptomatic, widespread or affects organ function, medical treatment with corticosteroids leads to improvement in most patients. Oral prednisone 20-40 mg per day is recommended with a gradual tapering regimen [44]. The optimal duration is unknown, but a minimum of 6-12 months seems reasonable. In the case of contraindication for corticosteroids, need for a corticosteroid-sparing therapy or corticosteroid-resistance, alternative agents such as hydroxychloroquine, methotrexate or azathioprine have been used, alone or in combination with corticotherapy. Of course, surgery or endoscopic procedures may be indicated in the case of obstructive uropathy especially when acute renal failure is present, when medical treatment is not efficient or when long-term fibrotic changes have occurred.

Patients with hypercalcemia should be encouraged to avoid excessive vitamin D supplementation, reduce exposure to the sun, and maintain a good hydration. Hypercalciuria and hypercalcemia usually respond to corticosteroids within a few days. Hydroxychloroquine and ketoconazole have also proved to be useful to lower calcitriol and calcium levels in patients with sarcoidosis [45]. Long-term effects of other therapies on the granuloma burden also helps limiting hypercalcemic complications of sarcoidosis.

In the case of testicular or epididymal involvement, protection of the patient's fertility must also be taken into account. Semen analysis at the time of diagnosis and sperm banking must be considered. Of note, corticosteroid treatment may sometimes [46] but not always [47] lead to improvement of the semen analysis.

Conclusion

In conclusion, urologic sarcoidosis is a rare form of extrapulmonary sarcoidosis. Direct granulomatous involvement of the urologic organs as well as indirect granulomatous or non-granulomatous involvement may affect virtually any component of the urologic tract. Sarcoidosis should be considered in the differential diagnosis of a wide range of urologic and urinary complaints in patients with known or suspected sarcoidosis, and may rarely be the presenting form of the disease. Urologists must also be aware that sarcoidosis may mimic most clinical and radiological features of primary malignancies of the urinary tract and lead to unnecessary surgery. Diagnosis is made on the basis of noncaseating granulomatous involvement, but exclusion of other granulomatous diseases is mandatory. The diagnosis is confirmed by the presence of sarcoid involvement of another organ. Corticosteroids remain the cornerstone of the therapy and surgery should be reserved mostly for obstructive uropathy or when an alternative diagnosis of malignant disease is contemplated.

References

1. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee (1999) Statement on sarcoidosis. *Am J Respir Crit Care Med* 160: 736-755.
2. [No authors listed] (1999) Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am J Respir Crit Care Med* 160: 736-755.
3. McGowan AJ Jr, Smith EH (1967) Urological implications of sarcoidosis. *J Urol* 97: 1090-1093.
4. Ricker W, Clark M (1949) Sarcoidosis; a clinicopathologic review of 300 cases, including 22 autopsies. *Am J Clin Pathol* 19: 725-749.
5. Muther RS, McCarron DA, Bennett WM (1981) Renal manifestations of sarcoidosis. *Arch Intern Med* 141: 643-645.
6. Goldsmith S, Harris M, Scherer K, Al-Quran S, Vorhis E (2013) Sarcoidosis manifesting as a pseudotumorous renal mass. *J Radiol Case Rep* 7: 23-34.
7. Boffetta P, Rabkin CS, Gridley G (2009) A cohort study of cancer among sarcoidosis patients. *Int J Cancer* 124: 2697-2700.
8. Svetec DA, Waguespack RL, Sabanegh ES Jr (1998) Intermittent azoospermia associated with epididymal sarcoidosis. *Fertil Steril* 70: 777-779.
9. Kodama K, Hasegawa T, Egawa M, Tomosugi N, Mukai A, et al. (2004) Bilateral epididymal sarcoidosis presenting without radiographic evidence of intrathoracic lesion: Review of sarcoidosis involving the male reproductive tract. *Int J Urol* 11: 345-348.
10. Patel H, Shaaban H, Kumar A, Modi T, Maroules M (2015) A rare case report of bilateral testicular masses as an initial manifestation of systemic sarcoidosis. *Urol Ann* 7: 378-379.
11. Carmody JP, Sharma OP (1996) Intrascrotal sarcoidosis: case reports and review. *Sarcoidosis Vasc Diffuse Lung Dis* 13: 129-134.
12. Askling J, Grunewald J, Eklund A, Hillerdal G, Ekblom A (1999) Increased risk for cancer following sarcoidosis. *Am J Respir Crit Care Med* 160: 1668-1672.
13. Tjan-Heijnen VC, Vlasveld LT, Pernet FP, Pauwels P, De Mulder PH (1998) Coincidence of seminoma and sarcoidosis: a myth or fact? *Ann Oncol* 9: 321-325.
14. Dick J, Begent RH, Meyer T (2010) Sarcoidosis and testicular cancer: A case series and literature review. *Urol Oncol* 28: 350-354.
15. Woolf R, Toms L, Mann B (2010) Systemic sarcoidosis mimicking advanced testicular cancer. *J R Soc Med* 103: 251-253.
16. Thuret R, Cariou G, Aerts J, Cochand-Priollet B (2008) Testicular sarcoidosis with elevated levels of cancer-associated markers. *J Clin Oncol* 26: 6007-6008.
17. Massarweh NN, Bhalani VK, Shaw KK, Crawford B, Lang E, et al. (2006) Testicular presentation of sarcoidosis and organ preservation: case report and review of management strategies. *Urology* 67: 200.
18. Massarweh NN, Bhalani VK, Shaw KK, Crawford B, Lang E, et al. (2006) Testicular presentation of sarcoidosis and organ preservation: case report and review of management strategies. *Urology* 67: 200.
19. Subik MK, Gordetsky J, Yao JL, di Sant'Agnese PA, Miyamoto H (2012) Frozen section assessment in testicular and paratesticular lesions suspicious for malignancy: its role in preventing unnecessary orchiectomy. *Hum Pathol* 43: 1514-1519.
20. Maurice MJ1, Zhu H (2013) Sarcoidosis of the prostate. See comment in PubMed Commons below *J Urol* 190: 711-712.
21. Brownstein PK, Mannes H, Bogaev JH (1975) Sarcoidosis and malakoplakia. *Urology* 6: 249-251.
22. Redewill FH (1943) Malakoplakia of the Urinary Bladder and Generalized Sarcoidosis, Striking Similarity of Their Pathology, Etiology, Gross Appearance and Methods of Treatment. *J Urol* 49: 401-407.
23. Wei H, Friedman KA, Rudikoff D (2000) Multiple indurated papules on penis and scrotum. *J Cutan Med Surg* 4: 202-204.
24. Rubinstein I, Baum GL, Hiss Y (1986) Sarcoidosis of the penis: report of a case. *J Urol* 135: 1016-1017.
25. Ho KL, Hayden MT (1979) Sarcoidosis of urethra simulating carcinoma. *Urology* 13: 197-199.
26. Carr LK, Honey RJ, Sugar L (1995) Diagnosis and management of urethral sarcoidosis. *J Urol* 153: 1612-1613.
27. Perimenis P, Athanasopoulos A, Barbaliis G (1990) Sarcoidosis of the ureter. *Eur Urol* 18: 307-308.
28. Mariano RT, Sussman SK (1998) Sarcoidosis of the ureter. *AJR Am J Roentgenol* 171: 1431.
29. Kalia V, Vishal K, Gill JS, Gill A (2010) Ureteric sarcoidosis--a rare entity. *Br J Radiol* 83: e247-248.
30. Hashimoto Y, Kudoh S, Yamamoto H, Hatakeyama S, Yoneyama T, et al. (2012) Sarcoidosis of the ureter. *Urology* 79: e81-82.
31. Fraioli P, Montemurro L, Castrignano L, Rizzato G (1990) Retroperitoneal involvement in sarcoidosis. *Sarcoidosis* 7: 101-105.
32. Gil A, Ofer Y, Yigla M, Goralnik L, Meretyk S, et al. (2010) Obstructive uropathy caused by retroperitoneal fibrosis presents as a late manifestation of sarcoidosis. *Ren Fail* 32: 1118-1120.
33. Fitzpatrick KJ, Chancellor MB, Rivas DA, Kumon H, Mandel S, et al. (1996) Urologic manifestation of spinal cord sarcoidosis. *J Spinal Cord Med* 19: 201-203.
34. Kim IY, Elliott DS, Husmann DA, Boone TB (2001) An unusual presenting symptom of sarcoidosis: neurogenic bladder dysfunction. *J Urol* 165: 903-904.
35. Sakaibara R, Uchiyama T, Kuwabara S, Kawaguchi N, Nemoto I, et al. (2001) Autonomic dysreflexia due to neurogenic bladder dysfunction: an unusual presentation of spinal cord sarcoidosis. *J Neurol Neurosurg Psychiatry* 71: 819-820.
36. Niedner R, Wokalek H (1985) [Disorders of potency caused by sarcoidosis]. *Hautarzt* 36: 563-565.
37. Pigott TA, Kellner CH (1987) Depression and sexual dysfunction complicating neurosarcoidosis. *JSC Med Assoc* 83: 16-18.
38. Spruit MA, Thomeer MJ, Gosselink R, Wuyts WA, Van Herck E, et al. (2007) Hypogonadism in male outpatients with sarcoidosis. *Respir Med* 101: 2502-2510.
39. Porter N, Beynon HL, Randeve HS (2003) Endocrine and reproductive manifestations of sarcoidosis. *QJM* 96: 553-561.
40. Inui N, Murayama A, Sasaki S, Suda T, Chida K, et al. (2001) Correlation between 25-hydroxyvitamin D3 1 alpha-hydroxylase gene expression in alveolar macrophages and the activity of sarcoidosis. *Am J Med* 110: 687-693.
41. Sharma OP (2000) Hypercalcemia in granulomatous disorders: a clinical review. *Curr Opin Pulm Med* 6: 442-447.
42. Rizzato G, Colombo P (1996) Nephrolithiasis as a presenting feature of chronic sarcoidosis: a prospective study. *Sarcoidosis Vasc Diffuse Lung Dis* 13: 167-172.
43. Casella FJ, Allon M (1993) The kidney in sarcoidosis. *J Am Soc Nephrol* 3: 1555-1562.
44. Iannuzzi MC, Rybicki BA, Teirstein AS (2007) Sarcoidosis. *N Engl J Med* 357: 2153-2165.
45. Ishii H, Igata F, Nabeshima K, Kushima H, Watanabe K (2015) Mediastinal Seminoma with an Elevated Level of Serum Angiotensin-converting Enzyme. *Intern Med* 54: 1909-1912.
46. Judson MA (2007) Extrapulmonary sarcoidosis. *Semin Respir Crit Care Med* 28: 83-101.
47. Conron M, Young C, Beynon HL (2000) Calcium metabolism in sarcoidosis and its clinical implications. *Rheumatology (Oxford)* 39: 707-713.

48. Canguven O, Balaban M, Selimoglu A, Albayrak S (2013) Corticosteroid therapy improves the outcome of semen analysis in an oligozoospermic patient with epididymal sarcoidosis. *Korean J Urol* 54: 558-560.
49. Hassan A, El-Mogy S, Zalata K, Mostafa T (2009) Bilateral epididymal sarcoidosis. *Fertil Steril* 91: 1957.