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Case report

A rare association of renal and neurosarcoidosis with minimal pulmonary involvement

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Abstract. Sarcoidosis is a granulomatous autoimmune disease with various clinical presentations predominantly affecting the respiratory tract. We report herein the case of a patient with autoimmune thyroiditis and vitiligo who presented with renal failure and symptoms of hypothalamo-pituitary dysfunction and was later diagnosed with both renal and neurosarcoidosis. He was treated with glucocorticoids and hydroxychloroquine with favorable response.

Key Words: renal sarcoidosis, neurosarcoidosis, Diabetes insipidus, autoimmune thyroiditis, vitiligo

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Introduction

Sarcoidosis is a multisystem disorder that can affect practically any organ of the body. The hallmark of sarcoidosis is the presence of noncaseating granuloma, a cluster of macrophages, epithelioid cells, mononuclear cells, and CD4+ T cells with a few CD8+ T cells in the peripheral zone (Thomas and Hunninghake 2003). The etiology of sarcoidosis is not known with certainty despite decades-long effort. It is generally thought that both genetic predisposition and environmental factors play essential roles in its pathogenesis (Ungprasert et al 2016; Chen et al 2008). Although the formation of non-caseating epithelioid granulomas can virtually occur in any organ and the clinical manifestations are protean, neurosarcoidosis is a relatively uncommon presentation of systemic sarcoidosis and its diagnosis is usually based on clinical and imaging findings. Concomitant involvement of extrapulmonary organs, such as kidneys is extremely rare and can be a useful occurrence for diagnosis as it may allow histopathological confirmation.

Case Presentation

A 55-year-old Caucasian male with a history of vitiligo, autoimmune thyroiditis and hypertension, recently diagnosed with diabetes insipidus, was referred to our Nephrology department for worsening renal failure. Six months prior to admission, the patient presented to a General hospital with fever, nonproductive cough, dyspnea, sweating and weight loss. Blood samples showed elevated inflammatory markers (C-reactive protein of 14 mg/dL, ESR of 52 mm/h), mild lymphopenia and normal serum creatinine and urea levels at that time. Screening for tuberculosis was negative. Chest X-ray and computed tomography (CT) showed non-specific, bilateral pulmonary sub- pleural millimetric nodules, inflammatory mediastinal adenopathies at the precarinary level and slight interstitial thickening in the lower lobes (Figure 1). He was diagnosed with acute interstitial pneumonia and received antibiotics with minimal favorable response. The patient was readmitted to the same hospital 3 months later for the persistence of cough and fatigue, as well as bitemporal headaches. This was accompanied by polyuria (7 L/day) and polydipsia. Laboratory tests excluded diabetes mellitus and were remarkable for inflammatory response (C-reactive protein of 48 mg/dL), and renal failure (creatinine of 2.38 mg/dL, urea of 121 mg/dL). He was diagnosed with diabetes insipidus by using the water deprivation test that showed a low urine osmolality after fluid deprivation. A contrast-enhanced brain magnetic resonance imaging (MRI) was delayed due to the elevated creatinine. The patient was commenced on oral desmopressin (60 mcg twice a day), and as a result the urine output gradually decreased to 2.5- 3 L/day, while the renal function declined.

At presentation to our Nephrology department, the patient's vital signs were normal. Besides the nonproductive cough, general fatigue and headaches, the patient had no other complaints and he was euvolemic. The consumption of toxins could not be identified and the patient wasn't on any medication at home. Laboratory tests disclosed persistent elevated inflammation markers (C-reactive protein of 39 mg/dL) and increasing serum creatinine (6.8 mg/dL, urea of 186 mg/dL). Electrolytes, corrected serum calcium levels, and parathyroid hormone were within normal range. Abdominal ultrasound showed both kidneys of normal sizes and a hyperechoic image of about 7 mm (microlithiasis) at the level of the right kidney; an obstructive etiology was excluded. Daily urine output was 3 L. Urine tests detected microscopic hematuria, proteinuria of 1 g/24 h (with normal proteinemia) and glycosuria (with normal calciuria).

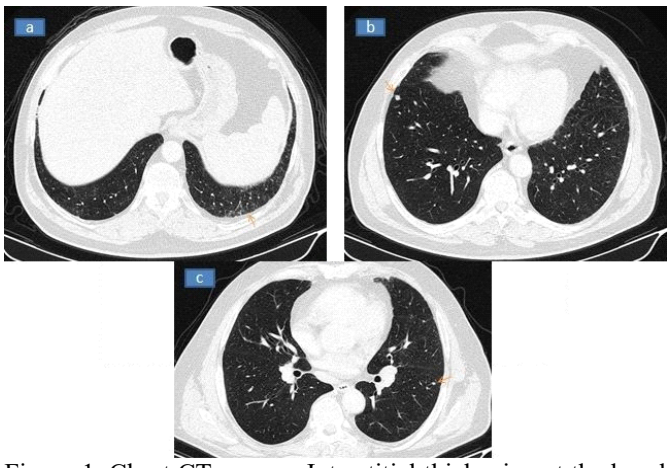

Figure 1. Chest CT scan. a. Interstitial thickening at the basal region of lower lobes (arrow). b, c. Non-specific, small pulmonary nodules with irregular distribution in upper and middle lobes bilaterally (arrows).

In order to identify the etiology of the intrinsic renal failure, we performed a screening for autoimmune (antinuclear antibodies, anti dsDNA antibodies, p-ANCA and c-ANCA, anti glomerular basement membrane antibodies), infectious (HBs antigen, anti HCV antibodies, anti-HIV antibodies) and neoplastic diseases (clinical exam, chest radiograph, abdominal ultrasound), which were all negative. Despite the fact that the patient had received intravenous volume (saline and 5% glucose), the serum creatinine values increased to 9.8 mg/dL after 2 days. Due to persisting high levels of creatinine and urea, microscopic hematuria and proteinuria, percutaneous renal biopsy was performed at 4 days after hospital admission. In light microscopy examination, no proliferation or deposits were found at the level of the mesangium, no thickening of the capillary walls and no extracapillary proliferation. However, the microscopy examination revealed marked atrophy of the renal tubules. Within the interstitium, a moderate diffuse lymphocytic infiltrate and epithelioid hystiocytes (CD 68 positive) formed imprecisely delimitated, non-necrotizing granulomas (Figure 2). The trichrome stain revealed moderate diffuse interstitial fibrosis. Immunofluorescence was negative for immune deposits. The histopathology report was compatible with renal sarcoidosis, in concordance with the patient's clinical history.

Subsequently, angiotensin-converting enzyme (ACE) activity was measured but showed normal values. Serum levels of 1,25 dihydroxivitamin D3 were decreased. The patient was initiated on glucocorticoids - pulse therapy with methylprednisone 1 g/day for 3 days, followed by oral methylprednisolone 48 mg/day. Serum creatinine values decreased from 9.3 mg/dL to 6.7 mg/dL within a week along with the remission of hematuria and proteinuria.

As soon as sarcoid granulomatous interstitial nephritis was diagnosed, further examinations were carried out to search for other possible locations of systemic sarcoidosis. Chest CT revealed minimal pulmonary involvement, symmetrical hilar lymph and unilateral paratracheal node enlargements. Pulmonary function tests were normal. Ophthalmologic examination showed no evidence of anterior or posterior uveitis. Electrocardiogram and cardiac ultrasound examination did not reveal any features of cardiac sarcoidosis. There were no liver function test abnormalities. The patient was referred to the rheumatologist for further

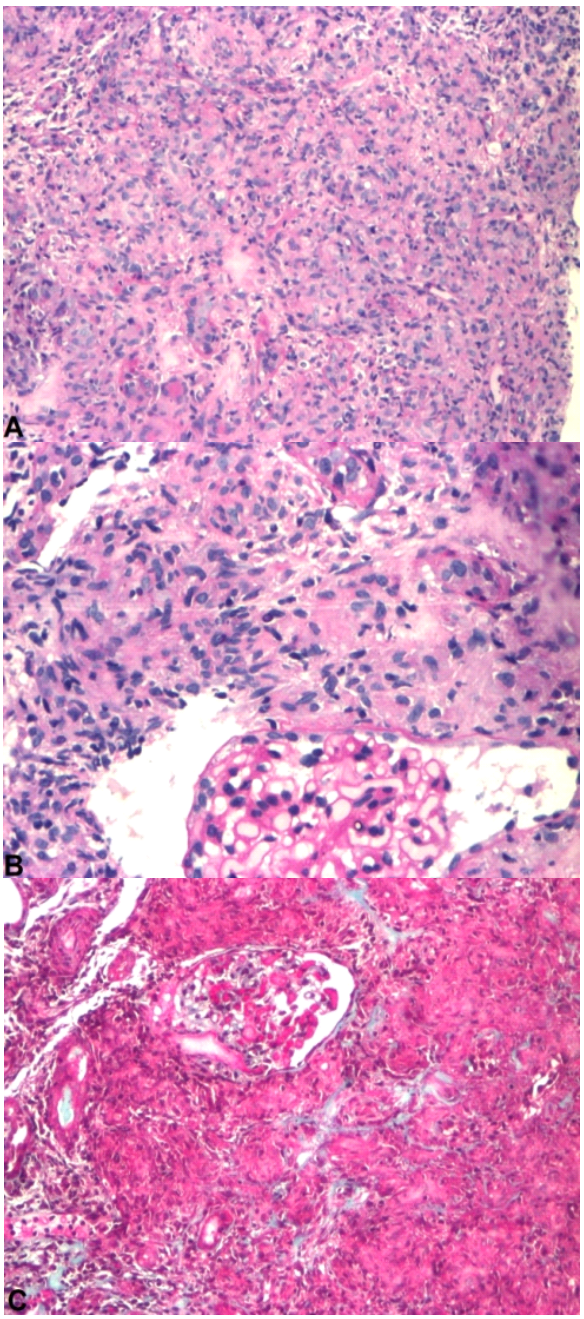

Figure 2. Kidney biopsy. a. Imprecisely delimitated, non-necrotizing granulomas surrounded by moderate diffuse lymphocytic infiltrate and epithelioid hystiocytes in the interstitium (PAS stain); b. Interstitial infiltrate with granuloma and normal glomerulus (PAS stain); c. Moderate diffuse interstitial fibrosis (Masson's trichrome stain).

evaluation. No musculoskeletal manifestations were identified, other possible causes of granulomatous disease were excluded and hydroxychloroquine 400 mg/day was associated as a steroid-sparing agent. At the endocrinological examination, water deprivation test and desmopressin test were performed. It was established that the diabetes insipidus is of central origin. The patient continued glucocorticoids and desmopressin with a daily diuresis of 2.5- 3 L.

At the three-month follow-up, weight gain and cushingoid features were noticed. Serum creatinine continued trending down to 2.2 mg/dL and the cardiac, ophthalmologic and rheumatologic

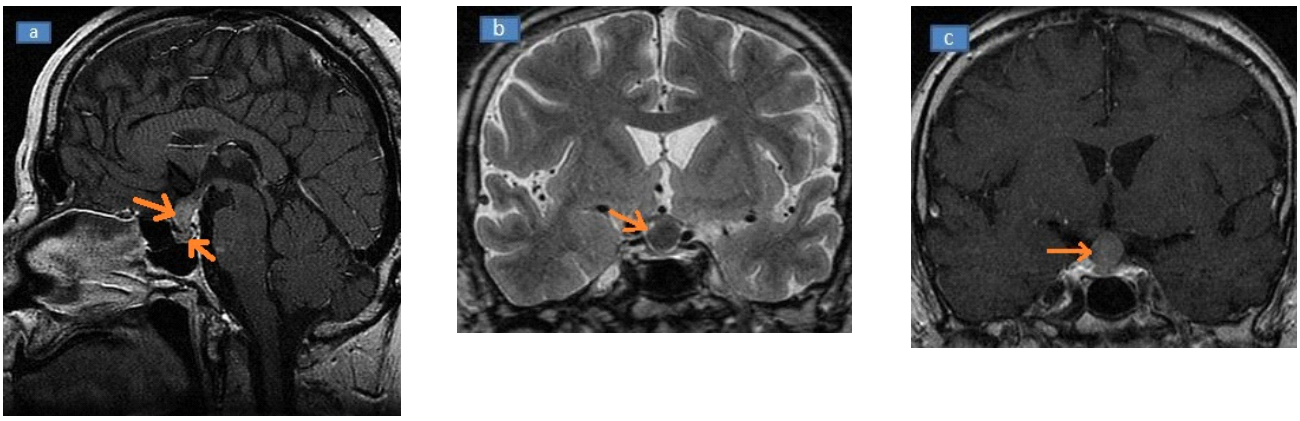

Figure 3: Contrast enhanced pituitary MRI. a. Infundibular mass displacing the normal pituitary gland inferiorly (arrows) b. Slight mass effect on the optic chiasm (arrow) c. Enhancement of the infundibular mass (arrow)

re- examinations were unremarkable. At the six-month follow-up, creatinine value reached 1.8 mg/dL and a contrast enhanced pituitary MRI was performed exhibiting infundibular thickening (11/12.8/15.5 mm) with gadolinium uptake and inferior displacement of the normal pituitary gland and slight mass effect on the optic chiasm (Figure 3).

The history of renal sarcoidosis correlated with the clinical picture and imaging findings were consistent with the diagnosis of hypothalamo-pituitary sarcoidosis, a form of neurosarcoidosis. The good renal response and the iatrogenic Cushing syndrome led us to the decision to taper the steroids to low doses of 8 mg/day. An attempt to discontinue resulted in an abrupt deterioration of the renal function with serum creatinine increasing to 6.2 mg/dL after two months. Consequently, the dosage of methylprednisolone was established back to 48 mg/day, with tapering of doses after 2 months.

At the 3-year follow-up, the most recent one in our clinic, the patient is on a low dose of methylprednisolone (4 mg/dl), with no clinical manifestations, creatinine decreased to 1.7 mg/dL and the patient remained free from dialysis.

Discussion

Sarcoidosis is a systemic granulomatous disorder that can affect any organ in the body, especially the lower respiratory tract. According to Mañá et al. the prevalence of nervous system involvement is 8.8% and that of the kidney is 2.7% in patients with extrapulmonary manifestations of sarcoidosis (Mañá et al 2017). The first mention of concomitant renal and neurosarcoidosis dates back to 1954 when it was described in a post-mortem report of a case of diffuse sarcoidosis with lung, liver, spleen, kidney and possibly pituitary gland involvement (Owen et al 1954). Since then, reports of larger cohorts of patients with both renal and nervous system involvement have been scarce, most of the studies highlighting only the lung, skin and eye manifestations of this disease. A epidemiological study of 27 patients with histologically proven renal sarcoidosis found only 2 cases (7.4%) to have central nervous system determinations (Löffler 2015). Likewise, another multicenter study which included 24 patients with hypothalamo-pituitary sarcoidosis found only 2 (8.3%) associations with renal sarcoidosis (Langrand et al 2012). In this report we described a patient who initially presented with nonspecific pulmonary symptoms, complicated with masked central diabetes insipidus and renal failure. He was diagnosed with biopsy-proven renal sarcoidosis while imagistic studies revealed concomitant minimal pulmonary involvement and neurosarcoidosis.

This case displays several important features: a rare association of renal and brain sarcoid determinations with minimal pulmonary involvement; normal levels of serum and urinary calcium, parathyroid hormone and ACE activity, decreased serum levels of 1,25 dihydroxivitamin D3; the development of severe renal failure due to granulomatous interstitial nephritis; the coexistence of other autoimmune disorders like vitiligo and autoimmune thyroiditis.

Renal biopsy performed on our patient revealed granulomatous interstitial nephritis with moderate fibrosis. This finding is considered to be the most typical histologic feature in patients with renal sarcoidosis. However, the progression to severe renal failure is rather unusual. The differential diagnosis for granulomatous renal lesions include drug-induced nephropaties, Wegener's granulomatosis, tuberculosis, Sjogren's syndrome or lupus erythematosus, all of which were excluded in this case.

Our patient presented neither hypercalcemia nor hypercalciuria, although unilateral microlithiasis was detected. Hypercalcemia and nephrocalcinosis is indeed considered the most common cause of chronic renal failure in sarcoidosis, but our patient only had microlithiasis. Measurements of ACE activity were normal in our patient, nevertheless, the largest retrospective series of patients with biopsy-proven renal involvement in sarcoidosis (47 patients) reported that serum ACE was increased in 55% of patients (Mahévas et al 2009).

Neurosarcoidosis represents an infrequent but severe organ involvement. Cranial neuropathy and meningeal involvement are the most common manifestations, but any part of the nervous system can be affected (Ungprasert and Matteson 2017). It can mimic many other diseases and in our case the diagnosis of renal sarcoidosis and the clinical symptoms suggested concomitant central nervous system localization. Hypothalamo-pituitary involvement is rare in sarcoidosis and represents <1% of all intrasellar lesions (Freda and Post 1999). MRI is considered the most accurate imaging technique for neurosarcoidosis and in our patient the enhancement and infiltrative aspect of the pituitary axis was compatible with sarcoidosis.

Glucocorticoids remain the cornerstone of treatment for patients with sarcoidosis. However, the optimal dose and duration of therapy for different localizations of this disease are unknown, as randomized controlled trials are lacking. Our patient was

started on methylprednisolone as soon as the diagnosis of renal sarcoidosis was established, with significant improvement of renal function and neurological symptoms. The attempt to withdraw glucocorticoids after 6 months resulted in a relapse of kidney injury manifesting as an abrupt increase of serum creatinine. Nevertheless, renal function soon improved after reinstitution of treatment. This clinical course is in concordance with many studies that show that patients with various sarcoid localizations have a high responsiveness to steroid therapy but often relapse when corticosteroids are withdrawn or tapered to low doses (Nozaki and Judson 2013). In patients who do not respond or cannot receive steroids due to adverse events, methotrexate, azathioprine, mycophenolate mofetil, leflunomide and anti-TNF agents can be acceptable options that have been reported to be efficient in case series. In a recent study of 24 patients with neurosarcoidosis, Infliximab was an effective treatment leading to remission or improvement in 70% of the cases. Nevertheless, the mortality rate in Infliximab-treated patients was substantial, indicating the severity of the disease and treatment-associated complications (Fritz et al 2020).

A relationship between sarcoidosis and autoimmune disorders has been suggested since the 1960s and a common immunopathogenesis has been proposed (Teilum 1964). Initially considered rare, sarcoidosis coexisting with other autoimmune diseases like autoimmune thyroiditis, diabetes mellitus, autoimmune hemolytic anemia, Sjogren's syndrome, vitiligo, celiac disease, is being reported with increasing frequency. The cases that described an association of autoimmune thyroiditis and vitiligo were linked to pulmonary and cutaneous forms of sarcoidosis (Demirkök et al 2007). To the best of our knowledge, this association of vitiligo and autoimmune thyroiditis with both renal and neurosarcoidosis is the first in the literature.

Conclusions

This case highlights a rare clustering of sarcoidosis with both renal and central nervous system involvement and autoimmune diseases represented by autoimmune thyroiditis and vitiligo. Clinicians should always be aware of the protean nature of sarcoidosis and thus reach an earlier diagnosis and treatment.

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