Renal Spectrum of Sarcoidosis

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Published Date: December 12, 2016

ABSTRACT

Sarcoidosis remains to be an enigma in contemporary medicine. Spectrum of renal manifestations of sarcoidosis is extensive and fascinating. Electrolyte abnormalities, including hypercalcemia and hypercalciuria can present in acute and chronic fashion. These can result in the development of acute neurological symptoms of confusion and neuromuscular disturbances and present in the form of chronic renal tubular dysfunctions. Parenchymal involvement of the kidney in sarcoidosis varies from chronic granulomatous interstitial nephritis to extensive spectrum of glomerular diseases, including membranous glomerulonephritis, crescentic glomerulonephritis, IgA nephropathy, focal segmental glomerular sclerosis, and minimal change disease. The mass-like appearance of renal sarcoidosis may mimic malignant tumors and lymphomas. Diagnosis of renal sarcoidosis requires exclusion of other conditions and thorough search for extrarenal manifestations to support it. Treatment of sarcoidosis includes controlling of electrolyte disturbances and immunosuppression for end-organ diseases. The unique immunological interface of the kidneys frequently dictates more aggressive and extensive immunosuppression to prevent relapse of parenchymal and glomerular diseases.
In this chapter, we review the epidemiology of renal sarcoidosis and diverse presentations of sarcoidosis encountered in medicine and nephrology practice. Thereafter, we will discuss the approach to the differential diagnoses of hypercalcemia and hypercalciuria. Later, we will describe the glomerular pathology encountered in patients with sarcoidosis. Finally, we will review the current literature on the treatment of hypercalcemia and use of immunosuppressive agents for interstitial and glomerular kidney diseases related to sarcoidosis.

**Keywords:** Renal Sarcoidosis; Hypercalcemia; Hypercalciuria; Glomerular Disease in Sarcoidosis

**DEFINITION AND INTRODUCTION**

Sarcoidosis is an autoimmune disease process characterized by granulomatous inflammation affecting multiple organ systems [1]. Respiratory system is generally the most commonly involved organ system in sarcoidosis, affecting up to 90% of individuals. Renal involvement of sarcoidosis can present as a variety of pathologies. Owing to the variety of renal presentations, an accurate percentage of the incidence of renal disease secondary to sarcoidosis has been difficult to estimate, in addition to the diverse definitions of what constitutes renal sarcoidosis. Nearly 50% of patients with sarcoidosis have some form of renal involvement. However, it is important to note that a renal disease may be the initial clinical manifestation that a patient with undiagnosed sarcoidosis presents with [2-5]. A better understanding of renal sarcoidosis is crucial to arrive at the correct diagnosis in a timely manner that could potentially prevent irreversible damages to the kidneys.

**ETIOLOGY AND PATHOGENESIS**

The underlying pathogenesis of sarcoidosis at the present state of medical science is not fully understood. A detailed summary of the current hypothesis for its pathogenesis has been summarized elsewhere and is not within the scope of this chapter. Genetics appeared to contribute to sarcoidosis development. The ACCESS study was a large multicenter NIH-funded case control study including over 700 patients and approximately 30,000 relatives. The study determined that these patients were almost 5 times more likely than the controls in the study to report a sibling or parent with sarcoidosis, suggesting a genetic component. However, attributable and absolute risks were around 1% [6-8].

**EPIDEMIOLOGY**

An accurate incidence of renal sarcoidosis has been difficult to estimate. This is partly because of the varying definitions of what exactly constitutes renal sarcoidosis. If the definition of renal sarcoidosis is strictly limited to interstitial renal granulomas, a review of previously reported case studies, including autopsies of patients with known sarcoidosis, has estimated the incidence to range from 7 to 23% [9,10]. Nephrocalcinosis, which is the most common cause of chronic kidney disease in this patient population, accounts for about 5% of patients with sarcoidosis [1,11,12]. If the definition is broadened to encompass renal abnormalities based on serum creatinine,
nephrocalcinosis, granulomatous interstitial nephritis (GIN), interstitial nephritis without granuloma, and IgA glomerulonephritis, then the estimate would be closer to 50% in patients with chronic sarcoidosis (excluding Lofgren’s syndrome) [11,13,14]. There are additional challenges in determining renal involvement in sarcoidosis as not every patient presenting with sarcoidosis undergoes a kidney biopsy for such purpose.

Hypercalcemia and hypercalciuria are sometimes considered 2 entities separate from the renal form of sarcoidosis. However, the role of the kidneys in these 2 entities would advocate the inclusion of these electrolyte imbalances under the umbrella term of renal sarcoidosis. The incidence of hypercalcemia has been generally thought to range between 10% and 20%, although some reported ranges have been as wide as 1.8 to 62.5% [15]. There are several confounding factors that hinder a truly representative range, and these include: varying definitions of hypercalcemia (with the most frequent definition being above 11 mg/dL calcium level), infrequent serum calcium measurement, and initiation of steroid therapy prior to serum calcium measurement. Hypercalciuria is the most common renal presentation and affects approximately 50% of patients with sarcoidosis when using the cutoff value of > 300 mg/24 h. However, a prevalence of 62% was found in a review series, in which a cutoff value of 200 mg/24 h was used [16].

**CLINICAL MANIFESTATIONS AND PATHOLOGICAL CHARACTERISTICS**

**Nephrolithiasis and Nephrocalcinosis**

In sarcoidosis, about 50% of patients have increased intestinal absorption of dietary calcium. The excess serum calcium is then excreted, resulting in hypercalciuria [12]. Those patients who absorb a greater amount of calcium or are unable to clear the increased calcium levels via renal excretion develop hypercalcemia. A case control study by Baughman et al. suggested that men are more likely to develop hypercalcemia compared to women [chi-square = 7.38, p < 0.01] [17].

Nephrolithiasis affects 10 to 13.8% of patients with sarcoidosis over the course of their disease [16,18]. Sometimes, individuals without a prior diagnosis of sarcoidosis can present solely with nephrolithiasis as the initial presentation of the underlying sarcoidosis. Nephrolithiasis was found to be the presenting clinical manifestation in 14 out of 618 patients (2.2%) in 1 prospective study [19]. In another 3-year prospective study involving 204 patients with sarcoidosis with a mean age 37 +/- 11 years, renal stones were the presenting manifestation in 4% of the cases [20].

Nephrocalcinosis is a condition related to the calcification of the renal parenchyma and tubules frequently associated with sarcoidosis among other disorders (Table 1). Advanced macroscopic disease often diagnosed by radiographic imaging studies in individuals suspected to have clinical and laboratory findings for sarcoidosis; however, such findings can be seen at times as an incidental finding in asymptomatic patients with otherwise unremarkable laboratory values. The diagnosis of the initial stages of nephrocalcinosis can be discovered through renal biopsy demonstrating
calcium deposits of either calcium phosphate or calcium oxalate on analysis (Figure 1). Calcium phosphate deposits will present as positive with von Kossa stain and will not show birefringence under polarized light. Patients may also complain of polyuria, which is thought to be mediated by diminished responsiveness of the antidiuretic hormone (ADH) secondary to hypercalcemia [21,22].

Table 1: Differential diagnosis of Nephrocalcinosis.

<table>
<thead>
<tr>
<th>Conditions with hypercalcemia and hypercalciuria</th>
<th>Conditions with hypercalciuria in the absence of hypercalcemia</th>
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<tbody>
<tr>
<td>• Primary hyperparathyroidism</td>
<td>• Distal renal tubular acidosis</td>
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<tr>
<td>• Vitamin D therapy</td>
<td>• Medullary sponge kidney</td>
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<td>• Milk alkali syndrome</td>
<td>• Neonatal nephrocalcinosis and loop diuretics</td>
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<td>• Congenital hypothyroidism</td>
<td>• Inherited tubulopathies</td>
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<tr>
<td>• Sarcoidosis</td>
<td>• Chronic hypokalemia</td>
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<td>• Other granulomatous diseases</td>
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Figure 1: Kidney biopsy. Light microscopy demonstrating focal calcifications in interstitium.

Granulomatous Interstitial Nephritis

GIN has been reported to occur from anywhere between 7 and 23% of patients with sarcoidosis. However, patients presenting with renal failure secondary to GIN are actually quite rare. Less than 100 cases have been reported in the literature, the first of which was reported by Berger and Relman in 1955 [23].
It would appear that sarcoid GIN has a male predominance. Sixty male patients out of 94 total patients (63.8%) were reported to have a sarcoid GIN. The mean presenting creatinine level was 4.8 mg/dL.

The urinary manifestations of interstitial nephritis are similar to those of other tubulointerstitial diseases. Urinalysis findings will be most commonly normal; however, these may show sterile pyuria, microscopic hematuria, glycosuria, and hypercalciuria [9]. GIN on histology usually reveals intact glomeruli and possible tubular injuries. The interstitium will have the presence of the classic noncaseating granulomas (Figure 2) as well as infiltrations predominantly from mononuclear cells. If the disease process is chronic, there may be evidence of fibrosis as well. The granulomatous infiltrate is not exclusive to sarcoidosis and is present in other disease processes [24-27] (Table 2). When compared to drug-induced interstitial nephritis where the infiltrate is along the cortico-medullary junction, the infiltrate in sarcoidosis is mainly confined to the renal cortex [9]. Urinalysis findings may show sterile pyuria, microscopic hematuria, glycosuria, and hypercalciuria.

**Figure 2:** Kidney biopsy. Light microscopy H&E stain. Noncaseating granulomatous interstitial nephritis related to sarcoidosis.
Table 2: Differential diagnosis of noncaseating granulomatous interstitial nephritis.

<table>
<thead>
<tr>
<th>Presence of Noncaseating Granulomas in Renal Interstitium</th>
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<tbody>
<tr>
<td>Sarcoidosis</td>
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<tr>
<td>Drugs: aspirin, gentamycin, allopurinol, ciprofloxacin</td>
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<tr>
<td>Tubular interstitial nephritis and uveitis (TINU)</td>
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<tr>
<td>Granulomatosis with polyangiitis</td>
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<tr>
<td>Foreign body giant cell reaction</td>
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<td>Infection: E.coli</td>
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<tr>
<td>Secondary to intravesical Calmetter-Guerin therapy for bladder cancer</td>
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<tr>
<td>Xanthogranulomatous pyelonephritis</td>
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<tr>
<td>Idiopathic</td>
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**Glomerular Disease**

Glomerular involvement is a rarer; however, there are glomerular diseases that have been linked to sarcoidosis. Membranous nephropathy is the most commonly implicated disease process where in 1 study of 33 patients with sarcoidosis and glomerular disease, 60% of patients had membranous nephropathy [28]. Another study involving 27 patients determined that 26% of patients had IgA nephropathy [29]. Other glomerular processes that have been associated with sarcoidosis include amyloidosis [30], crescentic glomerulonephritis [31], minimal change disease [32], and focal segmental glomerulosclerosis [33]. Therefore, several glomerular disease processes are associated with sarcoidosis, which need to be considered in the work up of glomerulonephritis.

**Renal Tubular Dysfunction**

Polyuria is the clinical feature associated with renal tubular dysfunction. Central and nephrogenic diabetes insipidus (DI) have both been implicated in sarcoidosis. In central DI, it is thought to be caused by a sarcoid lesion in the hypothalamic region. In nephrogenic DI, hypercalcemia interferes with ADH in 2 ways: 1) inhibits the binding of ADH to V2 receptors and 2) impairs the mobilization of intracellular aquaporins to the tubular cell apical membrane by inhibiting cyclic adenosine monophosphates [34]. It should be mentioned that nephrogenic DI due to sarcoidosis in the absence of hypercalcemia has been reported [35]; however, this is a rare entity.

Proximal or distal renal tubular acidosis secondary to tubular damage has also been noted in some patients. Proximal tubule dysfunction that presents with glycosuria, aminoaciduria, and phosphaturia, in addition to proximal renal tubular acidosis has also been described [36].

**Obstructive Uropathy**

Causes of obstruction represented by a variety of etiologies included renal stones, retroperitoneal lymph node enlargement, and retroperitoneal fibrosis, but rarely direct sarcoid involvement of the urethra, ureter, or bladder.
Bilateral hydroureteronephrosis secondary to extensive sarcoid-related expansion of the retroperitoneal lymph was successfully treated with corticosteroid therapy [37].

**Renovascular Disease**

The renal artery can be affected by sarcoid granulomatous inflammation as angiitis. This is a rare entity; however, when it is present, it can cause renal artery stenosis, which results in the development of secondary hypertension [38].

**Renal Radiographic Imaging of Sarcoidosis**

Ultrasound (US) and Computed Tomography (CT) are the preferred diagnostic modalities for nephrocalcinosis as they have sensitivity values of 85 to 90% and 81 to 86%, respectively [39]. However, a diagnosis of nephrocalcinosis by imaging does not necessarily indicate sarcoidosis. There are a variety of diseases that present with nephrocalcinosis, and these are summarized in Table 1. X ray of kidneys, ureters and bladder (KUB) was not as useful as other imaging studies as it has a sensitivity of only 63-66%. US and CT would also be useful in determining if any obstructive uropathy secondary to stones is present as well. Figure 3 demonstrates a US appearance of the kidneys in a patient with a biopsy-proven GIN. Figure 4 demonstrates the CT appearance of the kidneys in a patient with a biopsy-proven GIN. Magnetic Resonance Imaging (MRI) is not recommended as calcifications are poorly visualized using this modality [40]. Another imaging modality that can provide additional information is the Positron Emission Tomography (PET)-CT scan. This modality can not only remarkably detect sarcoidosis but also provide valuable information regarding disease activities after treatment initiation.

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**Figure 3:** Renal ultrasound (longitudinal scan) of patient with biopsy-proven noncaseating granulomatous interstitial nephritis from sarcoidosis demonstrates irregular contour of the kidney, increased cortical thickness and increase in echogenicity.
TREATMENT OF ELECTROLYTE DISORDERS AND RENAL DISEASES RELATED TO SARCOIDOSIS

Hypercalcemia and Hypercalciuria

Although not all cases of sarcoidosis present with hypercalcemia, the majority will have this electrolyte disorder.

Acute symptomatic hypercalcemia is normally treated in hospital settings with intravenous infusion of normal saline solutions. Loop diuretics need to be added to facilitate urinary calcium excretion via the thick segment of the loop of Henle. Calcitonin is rarely used for acute hypercalcemia owing to its short acting effect on extracellular calcium levels. The use of glucocorticoids is an essential step for the treatment of hypercalcemia related to sarcoidosis as they suppress intestinal absorption of calcium and 1-alfa hydroxylase in sarcoid granulomas [1].

Chloroquine with a dose of 200-400 mg can be used as an alternative treatment for hypercalcemia and for patients with sarcoidosis who cannot be treated with glucocorticoids. Ketoconazole 200-800 mg a day can be utilized as another non-prednisone alternative for the treatment of hypercalcemia [41]. The mechanism of action for both drugs is related to the suppression of 1,25 dihydroxy vitamin D production in granulomas.
The use of bisphosphonate for sarcoidosis-related hypercalcemia with elevated plasma 1, 25 dihydroxy vitamin D levels was reported to provide a rapid correction of plasma calcium levels without affecting vitamin D concentrations [42]. One has to realize that the use of bisphosphonates will alleviate hypercalcemia; however, it will not influence the disease progression.

Evaluation of a 24-h urine collection for calcium excretion is recommended in all patients with sarcoidosis [43]. Moreover, learning about the complete metabolic profile of the urine may provide valuable insights in the management of nephrolithiasis related to hypercalcemia and hypercalciuria in these patients.

Avoidance of thiazide-like diuretics is generally recommended for patients with hypercalcemia owing to its calcium-sparing properties. Limiting sunlight exposure is also advised to prevent the enhancement of vitamin D production [41].

**Treatment of Tubal Interstitial Diseases Related to Sarcoidosis**

In many patients with extrarenal manifestations of sarcoidosis, spontaneous remissions were reported. On the contrary, it is not commonly observed in tubulointerstitial or glomerular diseases related to sarcoidosis. Nevertheless, implementation of immunosuppressive therapy needs to be discussed in detail with the patients, addressing the potential side effects of immunosuppressive agents. The duration of therapy needs to be discussed as well [44]. Renal disease in sarcoidosis mandates kidney biopsy for appropriate tailoring of immunosuppressive therapy [45].

Owing to the rarity of renal sarcoidosis, many treatment strategies were extrapolated from pulmonary sarcoidosis management guidelines.

Prednisone is an effective first line therapy for patients with granulomatous tubulointerstitial nephritis related to sarcoidosis. The initial recommended daily dose of prednisone was 1 mg/kg/day [46,47]. The duration of therapy depends on the clinical response; however, it frequently requires progressive dose tapering over the period of several months to a year. Maintenance dose of prednisone is often necessary particularly in patients with multi-organ involvements with sarcoidosis. However, the optimal dose of prednisone to control multiple organ involvements is unclear. It was reported that renal sarcoidosis can flair in the process of prednisone tapering as a sole disease manifestation, while other organs will remain quiescent [48].

It was long recognized that tumor necrosis factor (TNF-α) play a significant role in granulomatous inflammation. Infliximab, an anti-TNF – αchimeric monoclonal antibody, was reported to be successfully used for the treatment of interstitial nephritis with noncaseating granulomas in conjunction with corticosteroid therapy tapering from 60 mg to none [49].

Remarkably, Granulomatous interstitial nephritis can recur in patients with kidney transplants, where the primary cause for end-stage renal disease (ESRD) was sarcoidosis [50]; while it is an extremely rare entity, successful treatment of the recurrence of granulomatous sarcoidosis in deceased kidney allograft recipients with the use of infliximab was reported [51].
Treatment of Glomerulonephritis Related to Sarcoidosis

Treatment of glomerular diseases as opposed to interstitial diseases related to sarcoidosis frequently required higher doses of immunosuppressive agents and longer duration of therapy. While corticosteroids continued to be the mainstay treatment for sarcoidosis, prednisone-sparing agents were utilized as well with different levels of success. Choice of the immunosuppressive agent should be personalized considering the variations of patients’ comorbid conditions.

Induction of immunosuppressive therapy with corticosteroids followed by maintenance therapy with mycophenolate mofetil demonstrated good clinical outcomes of remission maintenance [52].

Successful achievement of remission in case of crescentic necrotizing glomerulonephritis related to sarcoidosis with use of azathioprine along with prednisone therapy tapering was reported [53]. The recommended dose of azathioprine for renal sarcoidosis is 2 mg/kg/day [41].

The use of ACTH (Acthar®) was evaluated in the treatment of lung sarcoidosis with successful remission achievements [54,55]. Although such medication appears promising in treating renal sarcoidosis, no current literature to support or evaluate its effect is yet available.

Methotrexate is the antagonist of folic acid that was used for the treatment of severe tubulointerstitial and glomerular diseases related to sarcoidosis. Metabolism of methotrexate depends on renal clearance; therefore, it should be used for patients with relatively preserved renal function. Typical dose of methotrexate in sarcoidosis is 10-20 mg orally once a week. It is a slow acting medicine, which will preclude the rapid tapering of prednisone. Folic acid supplementation has to be an important part of the regimen [56].

Other agents, such as hydroxychloroquine, leflutamide, thalidomide, and rituximab may be used in rare cases where utilization of other agents is not practical or contraindicated.

The majority of patients with sarcoidosis are young people of the fertile age; therefore, an effective form of contraception needs to be discussed with female patients while being treated with immunosuppressive therapy to avoid teratogenic effects.

Treatment of Obstructive Uropathy

While cases of obstructive uropathy from sarcoidosis are uncommon, surgical treatment may be required to relieve such cases related to nephrolithiasis.

Prophylactic Antimicrobial Therapy and Immunization in Patients Treated with Systemic Immunosuppressive Agents for Renal Sarcoidosis

The use of systemic immunosuppression with 2 or more agents places patients at risk of opportunistic infections, such as toxoplasmosis, pneumocystis pneumonia, listeriosis, and nocardiosis. The use of trimethoprim-sulfamethoxazole double-stranded tablet 3 times a week is
the most common prophylactic therapy for the prevention of the abovementioned infections in patients without sulfa allergies.

Induction therapy in patients with systemic or renal limited sarcoidosis usually involves high doses of corticosteroids as opposed to T-cell depletion agents used in solid organ transplantation. Therefore, the use of antiviral and antifungal agents is not routinely recommended for prophylaxis in patients with sarcoidosis.

It is generally advised to avoid live virus vaccines in immunosuppressed individuals. Age-appropriate vaccination ideally needs to be accomplished prior to initiation of systemic immunosuppressive therapy.

**MONITORING OF DISEASE ACTIVITY**

A variety of tests have been proposed to assess active inflammation in sarcoidosis, including serum soluble interleukin (IL)-2 receptor and chitotriosidase. However, none of them are freely available in the present clinical practice. PET scanning appears to be quite sensitive in detecting disease activity; yet, it is not routinely utilized considering its costs.

Hypercalcemia, hypercalciuria, and vitamin D levels can be used as markers for disease monitoring. Monitoring of ACE levels as a marker of disease activity is not routinely recommended as it lacks sensitivity and specificity.

Degree of proteinuria and monitoring of serum creatinine levels while treating patients with glomerular and interstitial diseases will provide insights for disease remission or persistent activity.

**PROGNOSIS OF RENAL SARCOIDOSIS**

ESRD is a rare sequela of renal sarcoidosis. In 1 observational study, only 2(4.3%) out of 46 cases of sarcoidosis-related interstitial nephritis progressed to ESRD [47]. At a median follow-up of 24 months in that same study, approximately 66% of the patients had an estimated glomerular filtration rate (GFR) of < 60 mL/min/1.73m2. Nephrocalcinosis is less common than interstitial nephritis; however, it has a higher chance of progressing to ESRD. If the disease process is diagnosed before ESRD develops and patients are started on appropriate steroid and immunomodulator therapies, then patients will generally experience good recovery.

No significant amount of data regarding renal transplantation is present. A retrospective study investigated 18 patients from 8 French renal transplant departments. Ten of the patients had ESRD secondary to GIN, and the other 8 patients did not undergo biopsy. The median follow-up was 42 months. Five patients (2 patients had extrarenal involvement and 3 had renal involvement) experienced a recurrence of sarcoidosis. The renal recurrence occurred soon after transplantation with a median period of 13 months. The median GFR in the group of patients with renal recurrence was 31 mL/min/1.73m2, while that of the remaining patients in the study was 60 mL/min/1.73m2 [57].
In conclusion, while renal manifestations of sarcoidosis are not present in all patients, such manifestations are considered poor prognostic markers for spontaneous remission and commonly required prolonged immunosuppressive therapy durations. Attention to renal involvement in sarcoidosis may significantly modify the management of the disease.

References


