

## Urological Manifestations of Sarcoidosis

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### Abbreviations and Acronyms

CT = computerized tomography  
GIN = granulomatous interstitial nephritis  
PET = positron emission tomography  
RCC = renal cell carcinoma

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Nothing to disclose.

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**Editor's Note:** This article is the first of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 364 and 365.

**Purpose:** We describe the urological manifestations of sarcoidosis and how the disease may affect the management of multiple urological conditions.

**Materials and Methods:** We performed a PubMed® search using the query sarcoidosis and multiple urological terms.

**Results:** Sarcoidosis is a disease that has variable manifestations. There is often genitourinary involvement that is clinically silent. However, sarcoidosis may cause symptoms, such as nephrolithiasis, which are sometimes the first manifestation of the disease. Renal function may be affected, and appropriate recognition and treatment may avert progressive functional decline. The presence of sarcoidosis may also confound the diagnosis and staging of various urological malignancies, particularly renal and testicular carcinoma.

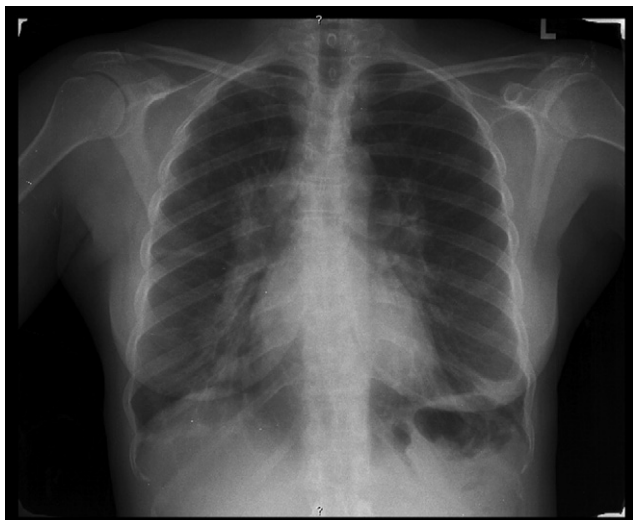
**Conclusions:** Urologists should be aware of the urological manifestations of sarcoidosis to avoid misdiagnoses and the over staging of urological cancers, and to identify when it is an underlying cause of nephrolithiasis or obstructive uropathy.

**Key Words:** sarcoidosis, hypercalciuria, granuloma

SARCOIDOSIS is a disease in which non-caseating granulomas form in various organs in the body, particularly the lungs and skin. The cause of this disease is still uncertain. Recent findings suggest that sarcoidosis may be due to a chronic immune response caused by exposure to common environmental factors such as propionibacteria, or airborne organic or inorganic material.<sup>1</sup> It may affect members of any race or gender. However, women are 30% more likely to be affected than men and African-Americans (36 per 100,000) are more commonly affected than Caucasians (11 per 100,000).<sup>2</sup> Sarcoidosis is not generally considered a urological disease and, therefore, is potentially overlooked as an etiology of various urological conditions. However, sarcoidosis is not rare. Its incidence is approximately equal

to that of bladder cancer at a rate of 21 per 100,000 ([www.seer.cancer.gov](http://www.seer.cancer.gov)), and it does cause problems that urologists treat such as nephrolithiasis. It also has manifestations that can mimic serious urological conditions such as testicular or renal masses. Furthermore, common manifestations of sarcoidosis such as PET positive lymphadenopathy can confound efforts to stage urological malignancies.

Most patients with sarcoidosis present before the age of 50 years, with the highest incidence in those 20 to 39 years old.<sup>2</sup> Although it often is detected by chest radiograph in asymptomatic patients, cough, shortness of breath or systemic symptoms such as fatigue or night sweats may be present (fig. 1). Of patients with sarcoidosis 90% have at least 1 of intrathoracic lymphadenopathy, pulmonary



**Figure 1.** Chest radiograph showing typical hilar lymphadenopathy of sarcoidosis.

involvement, or skin or ocular changes.<sup>2</sup> Skin manifestations can include macules, papules and/or plaques which may be single or multiple, and typically involve the face, posterior neck, upper back, trunk or extremities (fig. 2). Erythema nodosum is present transiently in nearly 10%, more often in women.<sup>3</sup> Most patients with sarcoidosis will experience remission and never require specific treatment for the condition. However, a third will experience chronic, potentially severe disease, and 1 in 20 will die of it.<sup>1</sup> Corticosteroids are the mainstay of treatment for those with persistent, symptomatic disease. In this review we will describe urological manifestations of sarcoidosis, and the manner in which sarcoidosis may interact with the diagnosis and treatment of multiple urological conditions.

## METHODS

A PubMed search was conducted using the terms “sarcoidosis” combined with other terms specific to urology, including “kidney”, “renal”, “ureter”, “hydronephrosis”, “bladder”, “carcinoma”, “pseudotumor”, “testis”, “urethra”, “calculus”, “penis”, “scrotum”, “urological” and “genital”. Relevant general, pathophysiological and demographic information was obtained from recent reviews.

## KIDNEY

### Nephrolithiasis and Nephrocalcinosis

Patients with sarcoidosis often have disordered calcium metabolism in the form of hypercalcemia or hypercalciuria due to activated macrophages in sarcoid granulomas expressing  $1\alpha$ -hydroxylase.<sup>4</sup> This activity leads to excessive circulating 1,25-dihydroxyvitamin D (calcitriol), resulting in enhanced

calcium absorption from the intestine.<sup>5</sup> The increased calcium load, which is worsened by excessive sunlight exposure or vitamin D ingestion, is excreted in the urine, causing hypercalciuria, which is present in up to 60% of patients with sarcoidosis.<sup>6</sup> The more severe state of hypercalcemia occurs in 10% to 20% of patients. Calcium supplementation in patients with sarcoidosis leads to worsened hypercalciuria.<sup>7</sup>

Nephrolithiasis has been reported to occur in 10% of patients, although hypercalciuria is not universally present when the calculus becomes symptomatic.<sup>5</sup> Importantly nephrolithiasis is sometimes the first sign of sarcoidosis.<sup>8,9</sup> In studies involving a careful review of patient histories, renal colic was the initial disease manifestation in 2.2% of patients.<sup>6</sup> However, sarcoidosis was diagnosed in only about half of the patients at the time of presentation with a calculus. Those who had delayed recognition presented later with evidence of chronic sarcoidosis. In these studies nearly all patients with sarcoidosis related nephrolithiasis had pulmonary involvement evident on chest x-ray and the majority also had palpable lymphadenopathy or cutaneous lesions. This combination of findings should suggest to urologists that patients with a calcium containing kidney stone who would otherwise be at low risk for nephrolithiasis, particularly African-American females, should undergo a physical examination and chest x-ray for signs of sarcoidosis. Nephrocalcinosis is less common than nephrolithiasis and is a result of chronic hypercalciuria.<sup>10</sup> It occurs in less than 5% of patients with sarcoidosis but it is present at a higher rate in those with renal insufficiency.<sup>5</sup>

The treatment of hypercalcemia and hypercalciuria in sarcoidosis is corticosteroids. They down-regulate the  $1\alpha$ -hydroxylase activity in macrophages, and normalize serum and urinary calcium levels.<sup>11</sup> Because hypercalcemia has a deleterious effect on renal function, steroid therapy usually improves impaired renal function as well.<sup>5,6</sup>

### Medical Renal Disease

Sarcoidosis also affects the kidneys directly through inflammatory infiltration of the tubular interstitium, leading to GIN. Occult involvement of the kidney is common in sarcoidosis, occurring in more than 20% of cases, but clinically evident involvement is much less common.<sup>4,5</sup> Renal impairment is more commonly caused by hypercalcemia and hypercalciuria.<sup>5</sup> However, several case series have reported renal insufficiency or failure in patients with normocalcemia without evidence of nephrocalcinosis.<sup>11</sup> These patients were found to have inflammatory infiltrates on renal biopsy that consisted of typical noncaseating granulomata. Most patients initially responded to corticosteroid therapy. Unfortunately a

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