The Protean Face of Renal Sarcoidosis

URSULA GÖBEL,* † RALPH KETTRITZ,* † WOLFGANG SCHNEIDER,† ‡ and FRIEDRICH C. LUFT* †

Franz Volhard Clinic, *First Department of Internal Medicine and †Department of Pathology, Klinikum Buch,
‡Medical Faculty of the Charité, Humboldt University of Berlin, Berlin, Germany.

Sarcoidosis received its name because the condition causes lesions that resemble a sarcoma. The disorder also goes by other names, such as lupus pernio, Besnier-Boeck-Schaumann disease, or more common, Boeck’s sarcoma. The disease involves primarily the reticuloendothelial system but affects all tissues and organs of the body. Sarcoidosis is a multisystem granulomatous disorder of unknown cause. The disease affects individuals worldwide and is characterized pathologically by the presence of noncaseating epithelioid granulomas in involved organs (1–3). Sarcoidosis typically affects young adults and usually presents with one or more of the following four abnormalities: bilateral hilar adenopathy, pulmonary infiltrates, skin lesions, and ocular involvement. In the United States, African Americans have a 2.4% lifetime risk of developing the disease, whereas in Caucasian Americans and Europeans, the incidence is lower. The immunogenetics of sarcoidosis has received attention. Kneitz et al. (4) observed sarcoidosis in monozygotic twins; however, no genetic inferences can be drawn from this report. Martinetti et al. (5) studied cohorts from Italy and the Czech Republic. They found positive and negative associations with various HLA markers in the two cohorts; the two patient groups in general yielded similar findings. Positive associations were found with HLA-A1, B8, and DR3 markers. Negative associations were identified for HLA-B12 and DR4. HLA-B27 was associated with pulmonary sarcoidosis. Maliarik et al. (6) recently reported on the natural resistance-associated macrophage protein (NRAMP1) gene in African Americans with sarcoidosis. Variants in this gene have been associated with pulmonary tuberculosis in several populations. The authors identified a variant associated with sarcoidosis, independent of the tuberculosis-associated variants previously described. The findings require confirmation. The organ most commonly involved (95%) is the lung. Pulmonary sarcoidosis is classified in terms of roentgenographic findings into three stages: stage I shows bilateral hilar adenopathy, stage II exhibits bilateral adenopathy and infiltrate, and stage III consists of interstitial disease and shrinking hilar nodes; stage IV is defined by advanced pulmonary fibrosis.

The cause of sarcoidosis is unknown, but an infectious cause seems plausible. Numerous microorganisms have been implicated, most notably mycoplasma and mycobacteria. Reports that sarcoidosis has been transmitted by cardiac and bone marrow transplantation support such a notion (7,8). A recent Japanese study implicated Propionibacterium acnes in 12 of 15 patients using the PCR. The remaining three patients in this study featured other species of Propionibacterium (9). Immunohistochemical staining has demonstrated that the majority of lymphocytes within the sarcoid granuloma are CD4+ T cells. However, the periphery of the granuloma is composed of CD4+ as well as CD8+ T cells (10). The broncho-alveolar lavage fluid generally shows a predominance of CD4+ T cells and results in an elevated CD4+ to CD8+ ratio (11). These CD4+ T cells bear surface markers of previous activation and have the ability to secrete spontaneously interleukin-2 (IL-2), interferon-γ, and other cytokines. Thus, CD4+ T cells and variants in the T-cell antigen receptor may be important in initiating and perpetuating sarcoidosis (12).

Several cytokines are important to granuloma formation and fibrosis. In addition to IL-2, IL-12 is involved in T-cell proliferation and activation. IL-6 and IL-8 also are elevated, as well as IL-15, a newly discovered cytokine produced by macrophages. IL-15 stimulates T and B cells and may trigger CD4+ T-cell production. In the course of the process, the Th1 lymphocyte profile shifts to a Th2 profile. As a result, various cytokines are released, such as IL-4 promoting matrix protein production, IL5 and IL13 stimulating IgE, and several chemotaxants (13). The dendritic cell recently received attention in the pathophysiology of sarcoideal reactions (14). These cells interact with T cells to provide both membrane-bound and soluble activation signals. Sarcoideal reactions may represent perturbations of dendritic cell function. Sarcoideal reactions are replete with immunologic phenomena, not the least important of which is the association with common variable immunodeficiency. As many as 10% of sarcoidosis patients develop common variable immunodeficiency (15).

Calcium Homeostasis, Nephrocalcinosis, Nephrolithiasis

Clinically important renal involvement is only an occasional problem in sarcoidosis (16). Particularly germane to nephrologists is the association of sarcoidosis with abnormal calcium homeostasis. Indeed, sarcoidosis can present as renal stone disease; the systemic diagnosis is not always obvious (17).
Activated pulmonary macrophages in sarcoidosis are capable of producing calcitriol. Probably all granulomatous disorders are associated with hypercalcemia. We recently described a patient with hypercalcemia and talc granulomatosis (18). In sarcoidosis, hypercalciuria may be present in half of cases, whereas 10 to 20% have hypercalcemia. The hypercalcemia is aggravated by sunlight and thus is more pronounced in spring and summer. Hypercalcemia should suppress the release of parathyroid hormone and the subsequent production of calcitriol by the kidney. In granulomatous disease, this lack of suppression suggests extrarenal, parathyroid-independent calcitriol production. Such production has been shown in activated mononuclear cells, notably macrophages in the lungs and lymph nodes (19–21). Normally, the macrophage synthesis of calcitriol is regulated by negative feedback to prevent excess production. In granulomatous diseases, the normal feedback control of calcitriol production is impaired. Interferon-γ seems to play a role in this resistance (22). Normocalcemic patients with sarcoidosis commonly are hypercalciuric (23). Increasing dietary calcium intake in these patients does not lower their calcitriol concentrations. Various treatment options are open. Patients with hypercalcemia generally respond to prednisone; those who do not may be treated with chloroquin, hydroxychloroquin, or ketoconazole (24,25). Ketoconazole acts by inhibiting several P450 enzymes, one of which is responsible for converting calcidiol to calcitriol (26).

Figure 1A shows a renal ultrasound examination of a 23-yr-old man who was evaluated for dementia (27). He had bilateral nephrocalcinosis, his serum calcium values ranged from 2.5 to 2.8 mmol/L, and his urinary calcium excretion was increased above the normal range. His parathyroid hormone concentration was suppressed, whereas his 1,25-dihydroxyvitamin D concentration was at the upper limits of normal at 56 ng/ml. A chest roentgenogram was normal, and a CT scan of the thorax disclosed normal pulmonary and hilar nodes, although other mediastinal nodes were increased in size. The dementia was explained by communicating hydrocephalus, which the patient developed because of neurosarcoidosis (28). The diagnosis was established by the biopsy of several lymph nodes, including one in the mediastinum. A representative section from this node is seen in Figure 1B. The patient had no proteinuria, and thus renal a biopsy was not performed. Corticosteroids improved the dementia and the hypercalcemia. Patients with sarcoidosis commonly have elevated angiotensin converting enzyme (ACE) concentrations (29). Like calcitriol, lysozyme, glucuronidase, and collagenase, the ACE is a product of epithelioid cells within the granuloma (3). Our patient’s ACE plasma concentration was twice the normal concentration.

We have reason to believe that the chronic hypercalcemia and hypercalciuria that accompany sarcoidosis can lead to renal insufficiency. A 63-yr-old patient was referred to us for chronic hypercalcemia, up to 3.3 mmol/L. He also had markedly decreased short-term memory and was mildly disoriented. A year earlier, coronary bypass surgery had been performed at another hospital. His chest roentgenogram showed chronic bilateral pulmonary fibrosis. The serum creatinine concentration was 3.8 mg/dl. The parathyroid hormone values were low, whereas the 1,25-dihydroxyvitamin D concentrations were elevated. The ACE activity was in the high normal range. A renal biopsy, shown in Figure 2A, showed chronic interstitial nephritis but without granulomatous changes. Bisphosphonates had been tried to no avail to lower his calcium concentrations. Corticosteroid administration reduced his serum calcium to 2.3 mmol/L, and his creatinine concentration decreased to 1.8 mg/dl. The patient’s wife recalled that a pulmonary biopsy had been performed years earlier in a third hospital and could recall the term “sarcoidosis.” We obtained a paraffin block of a mediastinal lymph node biopsy from that hospital, and the result is shown in Figure 2B.

Granulomatous Interstitial Nephritis

Approximately 20% of patients with sarcoidosis show granulomatous inflammation in the kidney (3). Granulomatous interstitial nephritis is common in sarcoidosis; however, the development of clinical disease manifested by renal insufficiency is unusual. Utas et al. (30) described a patient who had come to their attention because of mild edema and proteinuria.
Her creatinine clearance was 60 ml/min. The roentgenogram was normal as was a gallium lung scan. The renal biopsy showed typical noncaseating epithelioid granulomas with normal glomeruli. Drugs also can induce granulomatous nephritis. The patient described by Freitag et al. (27) had ingested nonsteroidal anti-inflammatory agents for several years. The distinction between granulomatous interstitial nephritis from sarcoidosis, drug hypersensitivity, or infection is not always straightforward (31). The authors made reference to ocular involvement in their patient. Presumably, their patient had uveitis. Tubulointerstitial nephritis and uveitis, also termed TINU syndrome, seems to be idiopathic. These patients should be evaluated for both sarcoidosis and Sjögren’s syndrome (32).

Granulomatous interstitial nephritis is shown in Figure 3A. The patient presented himself to other physicians 10 yr before admission with fever, submandibular lymph node swelling, and a widened mediastinum. Mediastinal lymph node biopsy secured the diagnosis of sarcoidosis, and a course of prednisone was initiated. Seven yr later, the patient again became febrile and developed cervical adenopathy and splenomegaly. He had a serum creatinine of 2.9 mg/dl, mild hypercalcemia, increased calcitriol concentrations, and an elevated plasma ACE level and excreted 1 g of protein in his urine daily. A renal biopsy secured the diagnosis. In Figure 3B, focal areas of calcification are shown within the renal parenchyma. A course of prednisone resulted in improvement of his renal function and calcium homeostasis. He currently receives maintenance prednisone and azathioprine. His creatinine concentration is stable at 1.3 mg/dl.

Shown in Figure 4 is a renal biopsy from a normotensive, nondiabetic, 53-yr-old man who was found to have a serum creatinine of 1.4 mg/dl on a routine examination. He also had microalbuminuria. A renal ultrasound revealed normal-sized kidneys. However, the study also showed a 1-cm diameter lesion in the right kidney, suggestive of renal cell carcinoma. At operation, this kidney and its small papillary adenocarcinoma were excised. The rest of the renal parenchyma was normal with the exception of scattered small granulomatous lesions. The granulomas contained occasional multinucleated giant cells of the Langhans type. No evidence of caseation was seen, and studies for Mycobacterium tuberculosis were negative. The chest roentgenogram was reviewed and judged to be normal. However, a CT scan of the thorax showed changes...
consistent with mild pulmonary fibrosis, although the hilar nodes were not enlarged. Hypercalciuria and hypercalcemia were not present, and the 1,25-dihydroxyvitamin D level was normal, although the ACE concentration was at the upper limits of normal. The patient reported not having taken any medication regularly. He specifically denied ingesting antibiotics or anti-inflammatory drugs. Postoperatively, the patient's serum creatinine concentration did not change. Renal sarcoidosis generally is treated with corticosteroids. We are undecided about which therapeutic recommendations would be best for this asymptomatic patient.

In our patient, granulomatous interstitial nephritis seems to be the sole clinical disease feature. Usually, pulmonary involvement is the clinical problem and the renal involvement is more difficult to detect (33). Decreases in renal function generally are mild or moderate in sarcoidosis. However, a patient with a rapidly progressive downhill course attributed to granulomatous interstitial nephritis from sarcoidosis has been described (34). Furthermore, two patients with nonglomerular interstitial nephritis and end-stage renal disease were reported (35). Thus, sarcoidosis cannot necessarily be considered a benign nephrologic condition.

Granulomatous interstitial nephritis generally is not caused by sarcoidosis. In a review of 1010 renal biopsies, Schwarz et al. (36) found six cases of granulomatous interstitial nephritis, all of which were caused by drugs. The same group discussed 76 documented cases of granulomatous interstitial nephritis in an earlier study and observed that a drug-related cause could be established in most cases (37). Half of the patients developed chronic renal insufficiency. Thus, the histologic diagnosis should suggest a drug- or medication-related cause until proved otherwise. The search for other causes may adversely delay the diagnosis.

Another aspect that our patient brings to mind is a putative association between sarcoidosis and urogenital malignancies. Marinides et al. (38) described a patient with a renal papillary adenocarcinoma with sarcoidosis in the same kidney. Our patient also had a papillary adenocarcinoma. The coexistence of sarcoidosis with hypernephroma has been described (39–41). Fukutani et al. (42) described a patient with transitional cell carcinomas in the bladder and renal pelvis. This patient also had renal sarcoidosis. The associations may be spurious. However, nephrologists should be aware that sarcoidosis is associated with renal tumors. The masses are not invariably malignant and have other causes. Notably, pseudotumors have been described (43,44).

**Glomerular Disease**

Glomerular involvement in sarcoidosis is not common, although focal segmental sclerosis, membranous glomerulonephritis, mesangio proliferative glomerulonephritis, mesangio capillary glomerulonephritis, IgA nephropathy, and crescentic glomerulonephritis all have been described (3), although their mechanisms are not known. Ig and complement deposition occasionally are observed. The mechanism by which glomerular injury occurs in sarcoidosis is not known, nor is a causal relationship to sarcoidosis proved. As an example, in one patient with sarcoidosis, crescentic glomerulonephritis and interstitial granulomas occurred in association with a positive antineutrophil cytoplasmic antibody titer, thereby confounding a possible relationship between the glomerular disease and sarcoidosis (45). In another, similar patient, Wegener’s granulomatosis was the presenting syndrome (46). The Wegener’s granulomatosis responded to cyclophosphamide treatment. The patient subsequently developed biopsy-confirmed pulmonary sarcoidosis months later. Conceivably, these two granulomatous disorders could have some common mechanisms.

Because sarcoidosis is associated with many immunologic deficiencies, a predisposition to glomerulonephritis from infectious causes in sarcoid patients might be expected. Michaels et al. (47) described two patients with sarcoidosis who developed active urinary sediments and nephrotic syndrome. Biopsies disclosed acute glomerulonephritis in these patients with hump-like epithelial deposits. One patient had recently had pneumonia, and the other had an elevated antistreptolysin O titer. In both patients, proteinuria and azotemia improved with corticosteroid therapy. An association between sarcoidosis and IgA nephropathy has been described relatively frequently. Taylor and Ansell (48) observed a sarcoidosis patient with IgA nephropathy and the ne-
phrotic syndrome. Corticosteroid therapy reversed the nephrotic syndrome. Nishiki et al. (49) observed a similar patient with sarcoidosis and IgA nephropathy. That patient also had thyroiditis. Corticosteroids reversed the nephrotic syndrome, the pulmonary manifestations, and the thyroid condition.

Membranous glomerulonephritis also has been encountered with sarcoidosis. Dimitriades et al. (50) described a 13-yr-old girl who presented with the nephrotic syndrome. Renal biopsy showed changes consistent with membranous nephropathy. Typical subepithelial deposits were found with electron microscopy. Bilateral hilar adenopathy was present, which suggested sarcoidosis. The diagnosis was confirmed by a bone marrow biopsy, which disclosed noncaseating granulomas. The patient was treated with corticosteroids and cyclophosphamide, and her condition stabilized. Khan et al. (51) described a 56-yr-old woman with pulmonary sarcoidosis who developed heavy proteinuria. A renal biopsy revealed both interstitial granulomas and membranous glomerulonephritis.

We recently encountered a 45-yr-old woman with massive proteinuria. A renal biopsy was consistent with membranous glomerulonephropathy and can be seen in Figure 5. In Figure 5A, the immunofluorescent pattern of granular IgG staining can be appreciated. The patient also had a nodular lesion on the left forearm. The lesion was biopsied and to our surprise revealed sarcoidosis. Figure 5B shows typical epithelioid granulomas. An asteroid body is visible. Corticosteroid therapy decreased the proteinuria and ameliorated the scan condition. Nephrotic syndrome with sarcoidosis also has been described in patients with minimal change disease. Mundlein et al. (52) had such a patient who also had Graves disease. Parry and Falk (53) observed an association between minimal change nephrotic syndrome and sarcoidosis.

Extracapillary glomerulonephritis associated with sarcoidosis is decidedly unusual (45,54–56). We encountered a 16-yr-old patient who presented with fever, joint discomfort, headache, weight loss, hypertension, and malaise. A chest roentgenogram shown in Figure 6A demonstrated bilateral hilar adenopathy characteristic of sarcoidosis. The patient had a serum creatinine level of 2.6 mg/dl and excreted 1.4 g/d protein in his urine. His urinary sediment showed dysmorphic erythrocytes and granular casts. The renal biopsy is shown in Figure 6B. Extracapillary crescent formation was found. Corticosteroid treatment led to regression of the hilar adenopathy and improvement in renal function. A second biopsy 1 yr later demonstrated regression of the crescents, although sclerotic glomeruli remained. Five yr later, the serum creatinine was 1.3 mg/dl. Fifteen yr later, the serum creatinine is 1.5 mg/dl and his BP is well controlled with medications.

Transplantation
Sarcoidosis certainly does not preclude transplantation. Kidneys, livers, hearts, lungs, and the combination of hearts and lungs have been transplanted successfully in sarcoid patients (57). The survival and complication rates are similar to other patients who undergo transplantation of these organs. Recurrence of pulmonary sarcoidosis has been reported after lung transplantation. The development of sarcoidosis in a patient with IgA nephropathy has been reported in a transplant recipient (58). Recurrent sarcoid granulomas in the kidney also have been reported in a sarcoid patient after transplantation (59); her corticosteroid dose was increased, and she improved.

Urinary Tract Disease
Retroperitoneal lymph nodes may enlarge sufficiently in sarcoidosis to cause obstruction. Sarcoidosis has even been shown to be responsible for bilateral hydronephrosis on the basis of retroperitoneal lymph node enlargement (60). Godin et al. (61) described a patient who presented with retroperitoneal fibrosis sufficient to compromise the right renal artery. Epithelioid granulomas consistent with sarcoidosis were found.

Summary
Sarcoidosis is a granulomatous disease of unknown cause involving the reticuloendothelial system and affecting all tissues and organs of the body. Sarcoidosis commonly involves the lungs, where it causes hilar adenopathy and pulmonary infiltrates. The skin and eyes also are common sites that come to the attention of clinicians. Ethnic and genetic propensities to
develop sarcoidosis exist, and cellular mechanisms are being studied intensively. Noncaseating granulomas are the major pathologic feature of sarcoidosis. The granulomas contain lymphocytes that are for the most part CD4+. Immune defects, particularly combined variable immunodeficiency, are common. The cause of sarcoidosis remains to be determined; an infectious cause has been postulated since the disease was first described but has not been secured convincingly. The kidneys may be involved in various ways. Because the granuloma epithelioid cells may produce calcitriol, sarcoid patients commonly have hypercalciuria, nephrocalcinosis, and stone disease and may develop hypercalcemia. The renal interstitium may be involved with granuloma formation, although adverse drug reactions should always be considered in the differential diagnosis. An association with renal neoplasms, notably papillary carcinomas, has been described. The glomeruli may be involved in sarcoidosis. IgA nephropathy, membranous IgG deposits, and even extracapillary crescent formation may occur. Proteinuria is variable but may be heavy. Sarcoidosis does not preclude transplantation, although the condition may recur. Because lymph nodes throughout the body may enlarge, ureteral obstruction and retroperitoneal fibrosis have been described. Sarcoidosis offers a challenge to the nephrologist and brings out the best of the internist in the subspecialist.

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References

Figure 6. (A) Roentgenogram showing bilateral hilar adenopathy. (B) Extracapillary glomerulonephritis with crescent formation. Magnification, ×500 (periodic acid-Schiff).


