# Renal Involvement in Sarcoidosis

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Sarcoidosis is a clinicopathologic syndrome resulting from dispersed organ involvement by a noncaseating granulomatous process of unknown cause. The clinical manifestations of sarcoidosis are protean, depending on the affected organs; however, the principal targets of sarcoidosis are the lungs and thoracic lymph nodes, which almost always are involved. As a rule, it is a disease of insidious onset that pursues a chronic course, with episodic remissions and exacerbations. The severity and diversity of its clinical manifestations depend on the extent of infiltrating granulomatous lesions of the involved organs and that of the number of affected organs. When diffuse and widespread the disease may pursue an acute fulminant course. Diagnosis depends on demonstration of the characteristic pathologic lesion of noncaseating granulomas within the affected organ.

Sarcoidosis is a common (1 to 40 cases per 100,000 population) disease of the relatively young (mean age 40 years), with a proclivity for racial (3.5 times more in blacks), ethnic (Scandinavian), and seasonal occurrence (summer rather than winter). Reports of community outbreaks, work-related risks, familial clustering, occurrence after organ transplantation, and experimental induction in animals by injection of affected tissue homogenates from humans strongly suggests an infective cause that remains to be identified.

Two associated metabolic abnormalities of diagnostic and clinical import are elevated levels of calcitriol (1,25-dihydroxy-vitamin $D_3$) and angiotensin-converting enzyme (ACE). Neither is unique to sarcoidosis. Elevated levels of calcitriol are consequent to the capacity of the infiltrating macrophages of the granulomas to synthesize calcitriol. Elevated levels of ACE are consequent to that of the multinucleated giant and epithelioid cells that ultimately develop in the granulomas, along with that of the infiltrating macrophages, to produce ACE. Of these, the elevated levels of calcitriol are the more important because they account for the abnormal calcium metabolism that occurs in most patients. Elevated levels of ACE are of no known clinical consequence

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and are of limited value in diagnosis; however, they can be useful in follow-up of the course of the disease and patient response to treatment.

In symptomatic cases, steroids are highly effective in suppressing the cellular inflammatory reaction of sarcoidosis and in reversing most forms of organ dysfunction caused by granulomatous infiltration. Therapy with prednisone (30 to 40 mg/d) for 8 to 12 weeks, with gradual tapering of the dose (10 to 20 mg/d) over 6 to 12 months, is usually sufficient. Persistent dysfunction can result from residual fibrosis after reversal of the active granulomatous lesions. Close monitoring of patients is essential during tapering and after discontinuation of steroid therapy, because 25% of treated patients experience relapse. Other drugs that have been used in cases unresponsive to steroids are methotrexate, chloroquine, azathioprine, and cyclophosphamide. Of these, methotrexate seems to be more effective.

The prognosis is worse in blacks, the elderly, and those patients who fail to respond to steroids or have extensive multiorgan involvement.

## Pathophysiology and Diagnosis

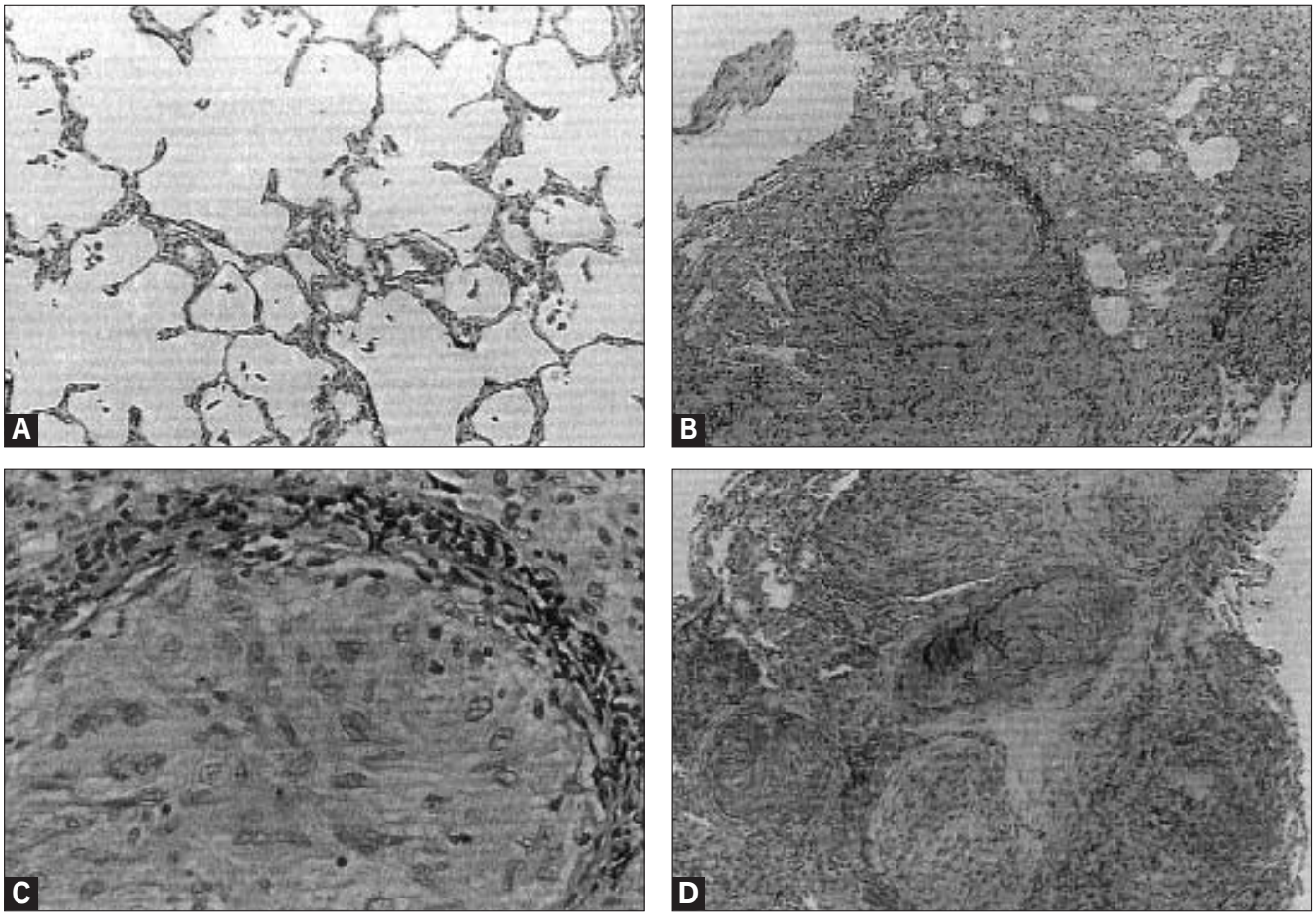


**FIGURE 8-1** (*see* Color Plate)

Pathology of granulomatous lesions in lungs affected by sarcoidosis. The diagnosis of sarcoidosis depends on demonstration of the characteristic lesion of noncaseating granulomas within the affected organs. As with other epithelioid granulomas, the more commonly involved organs are the lungs and liver. **A**, A section of a normal lung is shown. (Pentachrome stain × 10.) **B**, Multiple noncaseating granulomas and areas of mononuclear cell infiltration of the lung interstitium characteristic of sarcoidosis are shown. (Hematoxylin-eosin stain × 10.) **C** and **D**, Lesions in the lung are illustrated, showing their course from a cellular inflammatory response, which may be asymptomatic (*panel C*), to that of the fibrotic resolution (*panel D*). The fibrotic response usually accounts for the permanent loss of normal parenchyma and organ function. (Hematoxylin-eosin stain × 10 and pentachrome × 10, respectively.) (*From* Newman *et al.* [1]; with permission.)

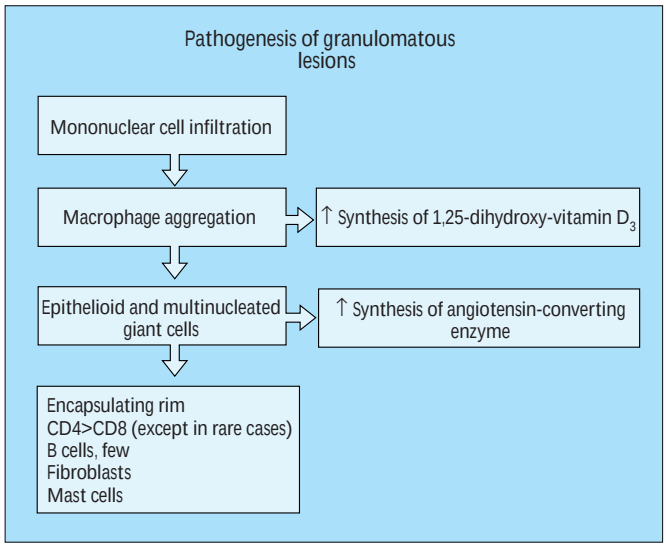


**FIGURE 8-2**

Pathogenesis of granulomatous lesions. Mononuclear cell infiltration is the initial step in the sequence of events that leads to granuloma formation. Recruited macrophages then differentiate into epithelioid and multinucleated giant cells. Activated lymphocytes are interspersed in the evolving lesion and come to form a rim around the granulomas. In time, fibroblasts, mast cells, and collagen fibers begin to encapsulate the mature sarcoid granuloma. Cultured granulomatous homogenates exhibit 1α-hydroxylase activity and are capable of converting 25-hydroxy-vitamin $D_3$ to its active 1,25-dihydroxylated form, calcitriol. This capacity resides in the infiltrating macrophages and is not unique to sarcoidosis but a feature of most other granulomatous disorders. Although lacking in specificity to be of diagnostic merit, radioactive gallium scans can be used as noninvasive methods of assessing the activity of sarcoid granulomas. The uptake of radioactive gallium by the macrophages and lymphocytes reflects the activity of the infiltrating cells in affected organs.

## CYTOKINES IMPLICATED IN PERPETUATING GRANULOMAS

- Interferon-γ
- Interleukin-2, 6, and 1β
- Chemoattractants
- Adhesion molecules
- Tumor necrosis factor-α

**FIGURE 8-3**

Cytokines implicated in perpetuating granulomas. Cytokines released by the infiltrating mononuclear cells and T-cell lymphocytes initiate the cascade of inflammatory reaction that results in subsequent formation of the noncaseating granulomas that characterize sarcoidosis. It is the loss of the otherwise balanced ability of cytokines to modulate the inflammatory response that accounts for the progression of the initial inflammatory reaction to granulomatous formation, and ultimately to the more detrimental process of fibrosis. Macrophages are critical in inducing fibroblasts to proliferate and deposit fibronectin and collagen in the extracellular matrix.

## SARCOIDOSIS FREQUENCY OF ORGAN INVOLVEMENT

| | Patients, % |
|---|---|
| Thoracic | 90–100 |
| Stage I: hilar adenopathy | |
| Stage II: hilar adenopathy plus pulmonary infiltration | |
| Stage III: pulmonary infiltration | |
| Dermatologic | 25 |
| Erythema nodosum, lupus pernio, papules, macules, plaques | |
| Ophthalmic | 25 |
| Uveitis, iritis, conjunctivitis | |
| Nervous system | 10 |
| Peripheral neuropathy, Bell's palsy | |
| Central nervous system | |
| Gastrointestinal | 40–70 |
| Liver | |
| Spleen | |
| Cardiac | 5–10 |
| Renal | 1–20 |
| Musculoskeletal | 10–15 |
| Polyarthritis, lower > upper | |

**FIGURE 8-4**

Frequency of organ involvement. Sarcoidosis is a multisystem disease. Parenchymal involvement by granulomatous lesions is most common in the lungs, whereas that of renal involvement is relatively rare.

## DIFFERENTIAL DIAGNOSIS OF PULMONARY SARCOIDOSIS

Sarcoidosis
Beryllium exposure
Hypersensitivity pneumonitis
Idiopathic pulmonary fibrosis
Mycobacterial infection
Fungal infections
Methotrexate-induced pneumonitis
Wegener's granulomatosis

**FIGURE 8-5**

Differential diagnosis of pulmonary sarcoidosis. The lungs are the principal organs involved in sarcoidosis. Pulmonary involvement may or may not be associated with hilar lymphadenopathy. In contrast to the pulmonary diseases listed, pulmonary symptoms may be absent in sarcoidosis even in the presence of extensive pulmonary lesions seen on chest radiographs. Pulmonary symptoms develop when the disease is in its late fibrotic phase and are associated with airway obstruction.

## LABORATORY FINDINGS IN SARCOIDOSIS

Hyperglobulinemia
Abnormal liver function tests
Anergy
Leukopenia
Hyperuricemia
Hypercalciuria
Hypercalcemia
Elevated calcitriol (1,25-dihydroxy-vitamin $D_3$)
Elevated angiotensin-converting enzyme
Cryoglobulinemia

**FIGURE 8-6**

Laboratory findings in sarcoidosis. The diagnosis of sarcoidosis depends on the demonstration of the characteristic pathologic lesion of noncaseating granulomas within the affected organs. Several laboratory abnormalities characterize sarcoidosis and are useful in supporting but not establishing the diagnosis. Hyperglobulinemia is a principal feature, being present in two thirds of cases. About half of patients have liver involvement, with some abnormality of liver function tests; anergy is present in about half of patients; leukopenia is present in 25% to 30%. Hypercalciuria is common because of increased levels of calcitriol. In 50% to 60% of patients levels of angiotensin-converting enzymes are elevated. Fever is present in about one third of patients.

## RENAL INVOLVEMENT IN SARCOIDOSIS

| | Patients, % |
|---|---|
| Calcium metabolism | |
| Hypercalciuria | 50–60 |
| Hypercalcemia | 10–20 |
| Nephrolithiasis | ≈10 |
| Nephrocalcinosis | 5–10 |
| Tubulointerstitial nephritis | |
| Granulomatous | 15–40 |
| Fibrotic | 10–20 |
| Glomerulopathy | Rare |
| Membranous | |
| Proliferative | |
| Focal segmental glomerulosclerosis | |
| Arteritis | Rare |
| Granulomatous angiitis | |
| Obstructive nephropathy | Rare |
| Retroperitoneal lymphadenopathy | |
| Retroperitoneal fibrosis | |

**FIGURE 8-7**

Renal involvement in sarcoidosis. The principal manifestations of renal involvement in sarcoidosis are the functional abnormalities resulting from the altered metabolism of calcium as a result of the increased synthesis of 1,25-dihydroxy-vitamin $D_3$ by the macrophages of the granulomatous lesions. The consequent increased calcium absorption from the gastrointestinal tract results in the hypercalciuria that can be detected in more than half of patients. The frequency of hypercalciuria depends on the extent of granulomatous lesions and on the time of the year, being more common in spring and summer when exposure to the sun is greatest. Hypercalcemia is less common and usually depends on coexistent deterioration of renal function when the capacity of the kidney to excrete calcium is compromised. In most patients, hypercalciuria is asymptomatic. Its principal manifestations are inability to concentrate the urine and polyuria. Nephrolithiasis occurs in about 10% of patients; another 10% develop nephrocalcinosis.

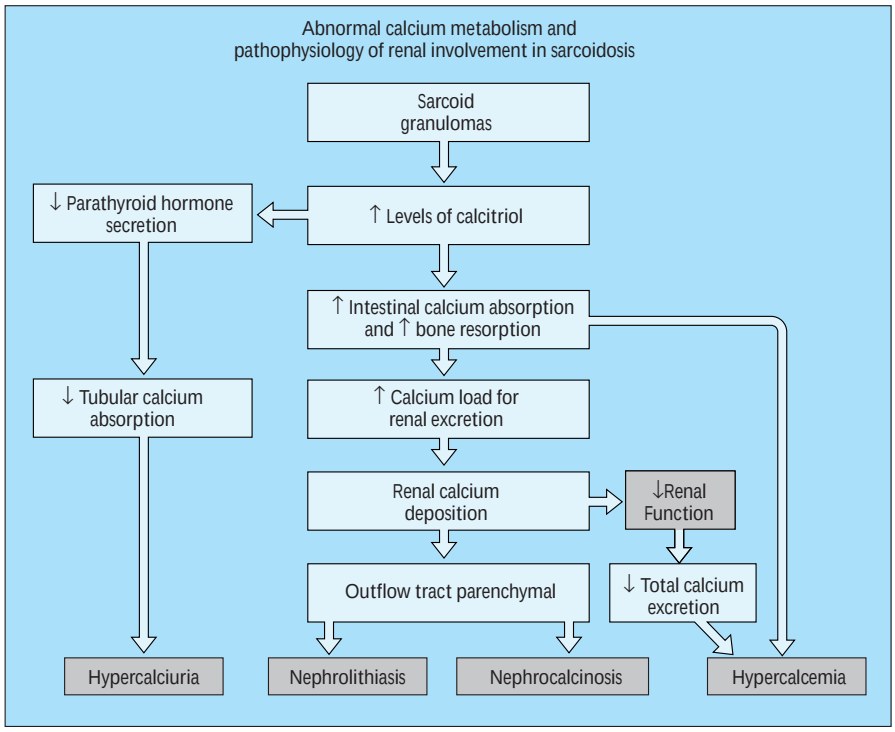


**FIGURE 8-8**

Abnormal calcium metabolism and pathophysiology of renal involvement in sarcoidosis. Increased synthesis of calcitriol (1,25-dihydroxy-vitamin $D_3$) by the macrophages of the granulomatous lesions of sarcoidosis are at the core of the abnormal calcium metabolism that accounts for the principal manifestations of renal involvement of sarcoidosis (*gray boxes*). Patients with hypercalciuria, which by far is the most common, may remain asymptomatic, and the disease may go undetected. Polyuria and a reduced capacity to concentrate the urine are its main manifestations. Either of these two features may be the result of tubulointerstitial nephritis caused by sarcoidosis, and can be present in the absence of any altered calcium metabolism. Nephrocalcinosis also may be asymptomatic. In contrast, nephrolithiasis presents as renal colic or hematuria. Hypercalcemia develops only when the load of calcium to be excreted exceeds the ability of the kidneys to excrete the calcium load, either because of reduced renal function or, less commonly, when the amount of calcium absorbed is excessive. The magnitude of hypercalcemia determines its symptomatology. The circulating level of parathyroid hormone should be determined in patients with hypercalcemia. An increase in the prevalence of parathyroid adenomas seems to occur in sarcoidosis. In hypercalcemia caused by elevated levels of calcitriol and by reduced renal excretion of calcium, parathyroid hormone levels should be negligible. Detection of elevated levels of parathyroid hormone should lead to the search for an adenoma. Patient management is directed at reducing calcitriol synthesis by treating the granulomatous lesions with steroids. Equally important measures in the management of such patients are restriction of calcium intake, avoidance of dietary supplements that contain vitamin D, shunning exposure to sunlight, and increased fluid intake.

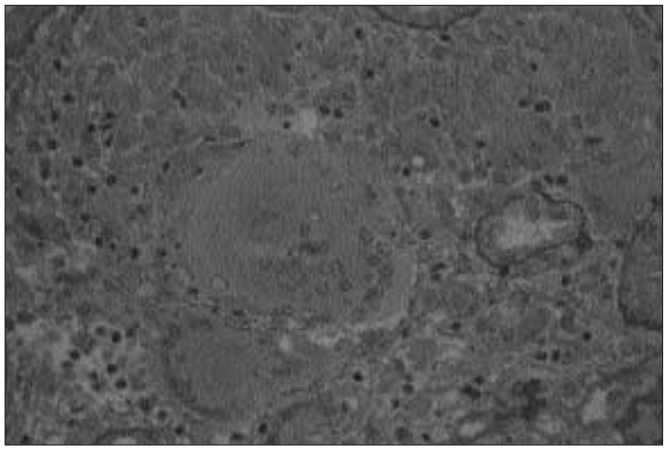

**FIGURE 8-9** (*see* Color Plate)

Micrograph of granulomatous lesions of the renal interstitium that are observed in 15% to 40% of patients with sarcoidosis. The highest rate reported in the literature is 40%. This figure is based on autopsy findings, which often reveal occasional granulomas of the kidney without any evidence of functional or clinical abnormality. The lower figure of 15%, or less, more clearly reflects diffuse infiltration of the kidneys with granulomas associated with clinical evidence of abnormal renal function, as shown here. Generally, enlarged kidneys are noted on renal ultrasonography.

**DIFFERENTIAL DIAGNOSIS OF GRANULOMATOUS LESIONS IN RENAL SARCOIDOSIS**

| Lesion | Patients, % |
|---|---|
| Drug-induced | 55–70 |
| Sarcoid | 5–10 |
| Wegener's granulomatosis | 5–10 |
| Other (less common): | |
| Tuberculosis | |
| Brucellosis | |
| Vasculitis | |
| Systemic lupus erythematosus | |
| Idiopathic | 15–20 |

**FIGURE 8-10**

Differential diagnosis of granulomatous lesions in renal sarcoidosis. Once considered rare, granulomatous interstitial nephritis is now observed in 10% of kidney biopsy results. Most of these are seen in cases of drug hypersensitivity. The commonly implicated drugs are antibiotics and nonsteroidal anti-inflammatory drugs. Sarcoidosis and Wegener's granulomatosis each account for 5% to 10% of cases observed on kidney biopsy. Other less common and rather rare causes include tuberculosis, angiitis, and lupus erythematosus. In some 15% to 20% of cases, the cause of the granulomatous lesions is never established.

## Clinical Course

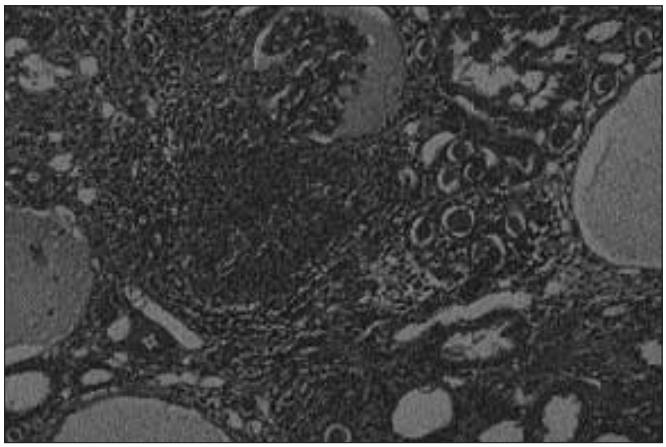

**FIGURE 8-11**

Micrograph of fibrosis. As a rule, abnormal renal function in patients with sarcoidosis is due to tubulointerstitial nephritis rather than granulomatous infiltration, which certainly is true in patients with progressive loss of renal function. Fibrosis may occur in the absence of granulomas but generally reflects the residual fibrosis of granulomatous lesions that have subsided or responded to steroid therapy. It is important to monitor renal function closely in such patients and initiate proper measures to retard the course of progressive renal failure.

As with all other forms of tubulointerstitial nephritis, tubular dysfunction is a common finding in such cases. The reduction in the glomerular filtration rate usually is modest but can progress to end-stage renal disease. Progression to end-stage disease tends to occur in older men who have minimal pulmonary involvement.

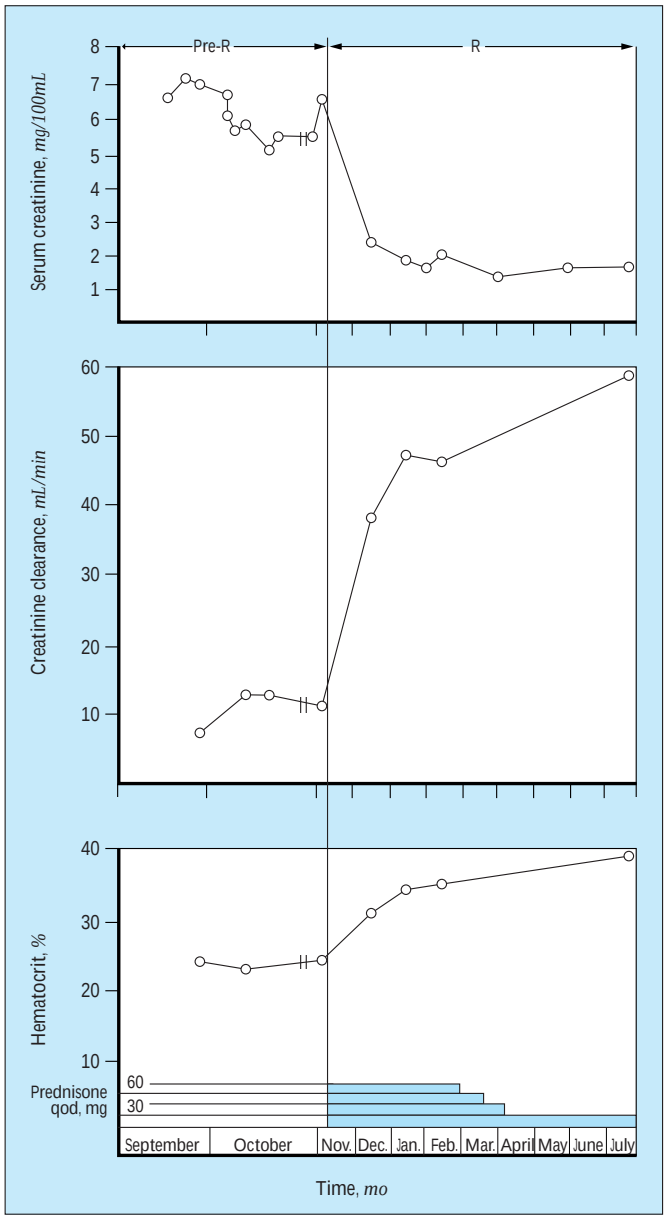


**FIGURE 8-12**

Clinical course of granulomatous nephritis. Extensive granulomatous infiltration of the kidneys can result in acute renal failure as a presenting clinical feature of sarcoidosis in the absence of any evidence of other organ involvement. As a rule, improvement in renal function occurs after steroid therapy (R), as shown here, in the clinical course of one such patient. (*From* Bolton *et al.* [2]; with permission.)

## CASE REPORT OF A PATIENT WITH SARCOIDOSIS HAVING RETROPERITONEAL FIBROSIS

### Patient profile

A man aged 40 years with established diagnosis of pulmonary sarcoidosis that had responded to steroids

Presentation: hypertension (200/140 mm Hg) and proteinuria (4 g/d)

Intravenous pyelogram: asymmetric kidneys with delayed appearance of contrast on right

Surgery: sclerotic matrix affecting aorta and proximal renal artery

Kidney biopsy: focal and global glomerulosclerosis, interstitial fibrosis

Postoperative course: persistent hypertension

**FIGURE 8-13**

Obstructive nephropathy due to sarcoidosis. Acute deterioration of renal function in sarcoidosis very rarely results from obstructive nephropathy caused by intrarenal granulomatous infiltrates or from extensive retroperitoneal lymphadenopathy or fibrosis causing obstruction of the renal vasculature or ureteral outflow [3,4]. (*From* Grodin *et al.* [3]; with permission.)

### CASE REPORT OF A PATIENT WITH SARCOIDOSIS HAVING GLOMERULOPATHY

**Patient profile**

A man aged 57 years with 3 months' history of progressive edema

Past history: pulmonary sarcoidosis, treated with steroids for 10 years, on 5 mg 4 times a day on admission

Physical examination: blood pressure, 180/95 mm Hg; peripheral edema

Laboratory test results: blood urea nitrogen, 32 mg/dL; creatinine, 4.3 mg/dL; albumin, 2.9 g/dL; cholesterol, 543 mg/dL; urinalysis, 6–8 erythrocyte/high-power field, 3 + protein; 24-h urine protein, 1.5 g

Kidney biopsy: membranous glomerulopathy; no granulomas

**FIGURE 8-14**

Sarcoid-associated glomerulopathy. Whereas renal involvement in sarcoidosis primarily is due to abnormalities of calcium metabolism and tubulointerstitial nephritis, rare cases of glomerulopathy have been associated with sarcoidosis. The detection of an abnormal urine sediment and proteinuria in a patient with sarcoidosis should always lead to consideration of glomerular disease. A variety of glomerular lesions have been reported in patients with sarcoidosis, including membranous glomerulopathy, minimal change disease, membranoproliferative glomerulonephritis, focal glomerulosclerosis, immunoglobulin A nephropathy, and crescentic glomerulonephritis. Of these, membranous glomerulopathy is more common. These rare cases may represent a chance coexistence of two separate diseases; however, their occurrence in a disease of altered immunity may reflect a causative association. Mesangial deposits of C3 have been observed in cases of sarcoid granulomatous nephritis in the absence of any clinical evidence of glomerular disease. Circulating immune complexes are detected in about half of cases of sarcoidosis in the absence of any evidence of renal involvement by granulomatous nephritis or glomerular lesions. As such, the presence of immune-mediated glomerulopathy may well be more than coincidental in occasional cases in which the patient may be predisposed by genetic or other as yet unidentified factors. (*From* Taylor *et al.* [5]; with permission.)

### CASE REPORT OF A PATIENT WITH RECURRENT GRANULOMATOUS SARCOID NEPHRITIS IN A TRANSPLANTED KIDNEY

| | |
|---|---|
| Aged 13 y | Sarcoidosis with pulmonary, hepatic, and ophthalmic symptoms<br>Responded to steroids<br>Steroids discontinued due to cataract and hypertension |
| Aged 19 y | Renal involvement progressive to end-stage renal disease<br>Cadaveric transplantation after 3 months of dialysis<br>Medications: azathioprine, 75 mg per day; prednisone tapered to 15 mg 4 times a day |
| Aged 26 y | Creatinine, 3.1 mg/dL; creatinine clearance, 20 mL/min; blood pressure, 150/84 mm Hg<br>Transplanted kidney biopsy: diffuse granulomatous infiltration<br>Treatment: prednisone increased to 60 mg/d for 6 wk<br>Response: creatine, 2.5 mg/dL; creatinine clearance, 35 mL/min |

**FIGURE 8-15**

Recurrent granulomatous sarcoid nephritis in a transplanted kidney. In patients with sarcoidosis having renal involvement whose renal failure has progressed to end-stage renal disease, kidney transplantation can be successful. However, due consideration should be given to the fact that recurrence of sarcoidosis in renal allografts have been reported. Conversely, documented cases exist in which sarcoidosis was transmitted by cardiac or bone marrow transplantation. This observation has been taken as evidence of an infectious or transmissible cause of sarcoidosis that highlights the problem of transplantation in patients with sarcoidosis. (*From* Shen *et al.* [6]; with permission.)

## References


1. Newman LS, Rose CS, Maier LA: Sarcoidosis. *N Engl J Med* 1997, 336:1224–1234.
2. Bolton WK, Atuk NO, Rametta C, *et al.*: Reversible renal failure from isolated granulomatous renal sarcoidosis. *Clin Nephrol* 1976, 5:88–92.
3. Grodin M, Filastre JP, Ducastelle T, *et al.*: Sarcoidosis retroperitoneal fibrosis, renal arterial involvement and unilateral focal glomerulosclerosis. *Arch Intern Med* 1980, 140:1240–1242.
4. Cuppage FE, Emmott DF, Duncan KA: Renal failure secondary to sarcoidosis. *Am J Kidney Dis* 1990, 11:519–521.
5. Taylor RG, Fisher C, Hoffbrand BI: Sarcoidosis and membranous glomerulonephritis: a significant association. *Br Med J* 1982, 284:1297–1298.
6 Shen SY, Hall-Craggs M, Posner JN, Shalozz B: Recurrent sarcoid granulomatous nephritis and reactive tuberculin test in a renal transplant recipient. *Am J Med* 1986, 80:699–702.


## Selected Bibliography


Casella FJ, Allon M: The kidney in sarcoidosis. *J Am Soc Nephrol* 1993, 3:1555–1562.

Romer FK: Renal manifestations and abnormal calcium metabolism in sarcoidosis. *Quart J Med* 1980, 49:233–247.

Fuss M, Pepersack T, Gillet C, *et al.*: Calcium and vitamin D metabolism in granulomatous diseases. *Clin Rheumatol* 1992, 11:28–36.

Hanedouche T, Grateau G, Noel LH, *et al.*: Renal granulomatous sarcoidosis: Report of 6 cases. *Nephrol Dial Transplant* 1990, 5: 18–24.