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## Sarcoidosis and Kidney Disease

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### 1. Introduction

Sarcoidosis is an illness of granulomatous inflammation with multi-organ association. While most individuals exhibit pulmonary pathology, renal involvement is not without prevalence or significance. This chapter will review the current epidemiology of the disease and explore the two major pathways in the pathogenesis of renal sarcoidosis, mainly granulomatous deposition and deranged calcium management. With these concepts addressed, further inquiries into intrinsic renal disease will be provided along with explanations of renovascular complications, obstructive nephropathy, and transplant pathology. Each ailment will be accompanied by common presentation, more detailed pathophysiology, appropriate diagnostics, and current treatment recommendations. This chapter will seek to purvey a comprehensive but concise exploration of renal sarcoidosis.

### 2. Epidemiology & susceptibility

Sarcoidosis can affect a wide range of racial and ethnic groups but it has high prevalence in northern European countries, Japan, and the United States<sup>1</sup>. Certain countries have skewed incidences, for example: black Americans are three times more likely than white Americans to develop the disease (Iannuzzi et al. 2007). However, across the racial and ethnic groups, females are more prone to the illness than males (Iannuzzi et al. 2007). The disease manifests itself typically in patients less than 50 years of age and mainly in the third or fourth decade of life (Iannuzzi et al. 2011). A patient with a first degree relative with the disease has a five-fold increase of developing sarcoidosis. Nevertheless, this risk still does not exceed 1% (Iannuzzi et al. 2011). Patient susceptibility also increases with certain associations of genetics and environmental factors. Discoveries into HLA gene products and the butyrophilin-like2 (BTNL2) gene are the latest areas of genetic interests (Iannuzzi et al. 2007). A variety of environmental triggers including wood-burning stoves, tree pollen, inorganic particles, insecticides, and mold have also been scrutinized in addition to mycobacteria and propionibacteria antigens (Iannuzzi et al. 2007, 2011). In fact, combinations of genetic and environmental activators have also been examined, for example: HLA-DQB1 and water damage or high humidity in the workplace (Iannuzzi et al. 2007). However, it seems that a ubiquitous number of agents may initiate a similar immunologic pathway that is pathognomonic for sarcoidosis.

### 3. Manifestations & pathogenesis

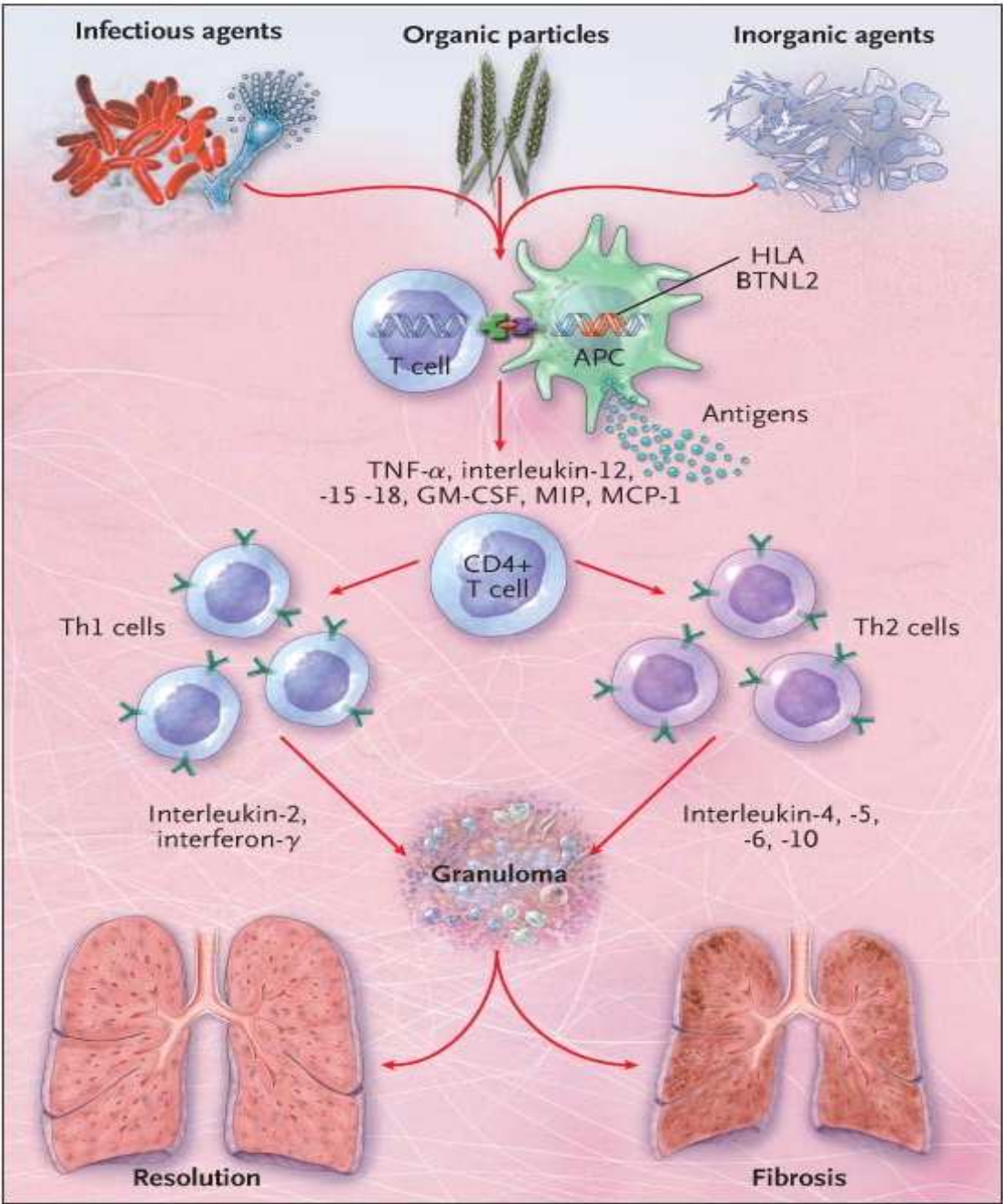
Sarcoidosis mainly affects the pulmonary system, with an over 90% occurrence rate in the afflicted, presenting as mostly hilar lymphadenopathy but also including pulmonary hypertension and obstructive and restrictive airway disease (Iannuzzi et al. 2011). Other major organ systems disturbed include the skin, the eye, the heart, and the nervous system with approximately 25 to 30% involvement (Iannuzzi et al 2011). Renal sarcoidosis is in fact rare with exact number relating prevalence difficult to come by. Unfortunately, the etiology for nephron-related disease is quite vast and it has been hard to delineate pure renal manifestations from simple metabolic disturbances (Berliner et al 2006). In order to understand the extent and pathogenesis of renal involvement, two central pathways for nephron insult has been validated including granulomatous deposition and deranged calcium management. While these pathways are by no means the only two routes of renal involvement, they are the most significant and the overriding themes for renal insult.

#### 3.1 Granuloma formation

Many aspects of this process still require elucidation yet strong evidence reveals that granuloma formation centers on T cells reacting with unclear triggers and certain gene products to illicit cascades that either lead to complete resolution of inflammation or to irreversible fibrosis (Iannuzzi et al. 2007). Specifically, antigen presenting cells including macrophages with susceptible HLA or BTNL2 gene products present triggers including organic, inorganic, and infectious agents to the CD4 T cell. Once initiated, numerous peripheral cytokines, interleukins, and immune modulators steer T cells into a T Helper 1 or T Helper 2 response; where with the former, resolution of inflammation is more probable but with the later, fibrosis and irreversible damage is more probable (Iannuzzi et al. 2007, 2011). This deposition of macrophages, giant cells, and T helper cells form the pathognomonic, non-caseating granulomas that defines sarcoidosis (Casella and Allon 1983) See Figure 1. In renal disease, these granulomas are primarily in the cortex but may also be found in the medulla or capsule (Casella and Allon 1983). This process is the basis for granulomatous interstitial nephritis, which will be further discussed subsequently.

#### 3.2 Deranged calcium management

Despite the granulomatous inflammation that marks sarcoidosis, deranged calcium homeostasis has a greater effect on the kidneys than the invasive granulomas themselves. Activated pulmonary macrophages express 1- $\alpha$  hydroxylase, which has important implications in maintaining appropriate levels of calcium in the body. In normal physiology, calcium balance is attained through the intricate interactions of parathyroid hormone (PTH), calcium, phosphorus, and Vitamin D. PTH upregulates renal 1- $\alpha$  hydroxylase, a cytochrome P450 enzyme located in the proximal tubule, to metabolize 25-hydroxy vitamin D to 1, 25-dihydroxy vitamin D, the bioactive form of Vitamin D, also known as calcitriol. Calcitriol, in turn, promotes calcium absorption in the intestines, kidneys, and bones. When calcium levels are adequate, normal physiological negative feedback mechanisms halt the PTH and calcitriol cycle. However, in sarcoidosis, extra-renal production of 1- $\alpha$  hydroxylase inappropriately increases calcitriol levels thereby increasing serum calcium and decreasing PTH. Unlike its renal equivalent, the granulomatous 1- $\alpha$  hydroxylase is immuned from the normal negative feedback mechanisms of hypercalcemia and is therefore unregulated,



(Iannuzzi MC et al. N Engl J Med 2007;357:2153-2165.)

Fig. 1. Hypothesized Immunopathogenesis of Granuloma Formation.

causing disturbed calcium homeostasis. This not only causes hypercalcemia, hypercalciuria and possibly subsequent nephrolithiasis and nephrocalcinosis, which itself is the most common cause of progressive renal failure. The clinical consequences of each imbalance range from trivial presentation to overt pathology including dehydration, renal colic, and end-stage renal disease. Diagnosis may be established by laboratory findings, ultrasonography, and computed tomography. General treatments incorporate adequate oral hydration, minimization of dietary calcium and vitamin D, avoidance of UV light exposure, and possibly corticosteroid therapy (Sharma 1996).



Hypercalcemia may cause decrease glomerular filtration rate by vasoconstricting the afferent arterioles and thereby decreasing renal blood flow (Berliner et al 2006). Additionally, it may cause tubular necrosis, tubulointerstitial non-granulomatous inflammation with calcium deposits ultimately causing nephrocalcinosis and chronic kidney disease (Berliner et al 2006). Hypercalciuria, which is three times as more common as hypercalcemia, predisposes patients to calcium oxalate nephrolithiasis, which may ultimately lead to obstruction or chronic pyelonephritis (Berliner et al 2006 and Sharma 1996). Renovascular complications as well as obstructive nephropathy will also be further discussed subsequently.

#### 4. Obstructive nephropathy

Abnormal calcium metabolism is a well known feature of sarcoidosis. Hypercalcemia and hypercalciuria is related to endogenous vitamin D. It is suggested that excess vitamin D may result in increased intestinal calcium absorption and consequent hypercalcemia, hypercalciuria and renal calculi. Hypercalciuria is defined as using excretion of 300 mg/day in men or 250 mg/day in women, about 2-5% healthy adults exhibit hypercalciuria. Hypercalciuria is the most common renal manifestation. It is caused by glomerular filtration of excess blood calcium and suppression by high calcitriol levels on PTH activity. It affects 50% of patients with sarcoidosis, often with an insidious onset because most patients remain normocalcemic. Sharma suggests that 10% of patients with sarcoidosis are diagnosed with hypercalcemia whereas 30% of patients with sarcoidosis show an increase in serum calcium. (Sharma, 1996)

In 1988, Foster described eight patients where he described extra uveitis may be the presenting sign of sarcoidosis. It was the first study that suggested that there may be unexpected presenting signs of sarcoidosis. (Foster, 1988) One of these symptoms may be nephrolithiasis. In a study from Italy, the charts 618 patients with histologically proven sarcoidosis was reviewed in 1978-92 in order to identify nephrolithiasis as a presenting feature of sarcoidosis. (Rizzato et al 1995) The authors concluded that calculi were the presenting feature of sarcoidosis in 6 out of 618 patients (1%) and was the first manifestation of disease in 14 (2. 2%) of the patients. In another 9 patients who presented with pulmonary involvement, persistent hematuria or pyuria led to discovery of stones via ultrasound or intravenous pyelography. Given that this is an uncommon disease, there is a very small chance that a physician seeing a patient for the first time with a new kidney stone will later prove to be is sarcoidosis. In the literature, the overall prevalence of nephrolithiasis is 10% in patients with sarcoidosis. (Muther et al 1981 and Rizzato 1995) The incidence of 2.2% exceeds more than 20 times the expected yearly rate of renal calculi in the general population (36 per 100, 000 in women and 123 in men in Rochester (Johnson et al 1979), 122 in California (Hiatt et al 1982) and 68 in Kyoto -Osaka. (Yoshida and Okada, 1990) In course of chronic sarcoidosis, approximately 10-13.8% of patients have at least 1 asymptomatic stone. (Lebacqz, 1970)

Treatment of hypercalciuria involves minimization of dietary calcium and Vitamin D, avoidance of UV exposure, and dietary oxalate restriction. This is because an increase in intestinal calcium absorption caused by excess in 1, 25 dihydroxyvitamin D may result in an increase in urinary oxalate excretion especially if diet is low in calcium. Overabsorption of calcium leaves less of this divalent cation to complex with oxalate in the proximal intestine so more oxalate is delivered to the colon in which anion is hyperabsorbed. Corticosteroids

are usually necessary to normalize these parameters as they can decrease inflammatory activity and reduce calcitriol syntheses.

Retroperitoneal lymph nodes can enlarge sufficiently to cause urethral obstruction.

(Frailly et al 1990). Sarcoidosis has also been shown to be responsible for bilateral hydronephrosis on the basis of retroperitoneal lymph node enlargement, with resolution after corticosteroid treatment. (Miyazaki 1995).

## **5. Glomerular diseases associated with sarcoidosis**

Glomerular involvement in sarcoidosis is not very common. The spectrum of commonly reported glomerular diseases include focal segmental sclerosis, membranous glomerulonephritis (GN), mesangioproliferative glomerulonephritis, mesangiocapillary glomerulonephritis, IgA nephropathy and crescentic glomerulonephritis. (Sheffield 1997) The exact mechanisms of glomerular disease in sarcoidosis are not known. Due to the absence of a consistent glomerular pathology and a well described etiological pathway, most cases are believed to be coincidental associations. Broadly speaking, abnormalities in both the humoral and cellular immune system in sarcoidosis contribute to the development of immune complex -type glomerulonephritis which also explains why immunoglobulin and complement deposition are commonly observed in renal biopsies in sarcoidosis. (Gobel et al 2001).

### **5.1 Membranous glomerulonephritis**

Overall, membranous glomerulonephritis (MGN) is the most commonly reported glomerular pathology. Amongst 39 cases of glomerular diseases reported in sarcoidosis, Vanhille et al found that 13 were MGN, largely occurring late in the course of overt disease. (Vanhille et al 1986) Khan et al. described a 56-yr-old woman with pulmonary sarcoidosis who developed heavy proteinuria. A renal biopsy revealed both interstitial granulomas and membranous glomerulonephritis. (Khan et al 1999) Rarely patients may be diagnosed to have sarcoidosis during the work up for secondary causes of nephrotic syndrome. Dimitriades et al. described a 13-yr-old girl who presented with the nephrotic syndrome and renal biopsy showed membranous nephropathy. (Dimitriades 1999) 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. In an experimental study, Maruyama et al, induced subepithelial deposits in pigs injected with heterologous antibodies to angiotensin converting enzyme (ACE). Confocal microscopy showed co localization of the granular deposits of ACE and anti ACE goat IgG on the outer aspect of glomerular basement. The authors conjectured that a similar autoimmune process may cause membranous GN in sarcoidosis. While traditionally idiopathic MGN is steroid resistant, most cases of MGN associated with sarcoidosis seem to respond to high dose steroid therapy especially if there is coexistent granulomatous interstitial nephritis (GIN) (Khan et al 1999). Others used pulse methylprednisolone plus oral cyclophosphamide to show remission of the nephrotic state. (Dimitriades et al 1999) See Figure 2. for histology of membranous nephropathy in sarcoidosis.

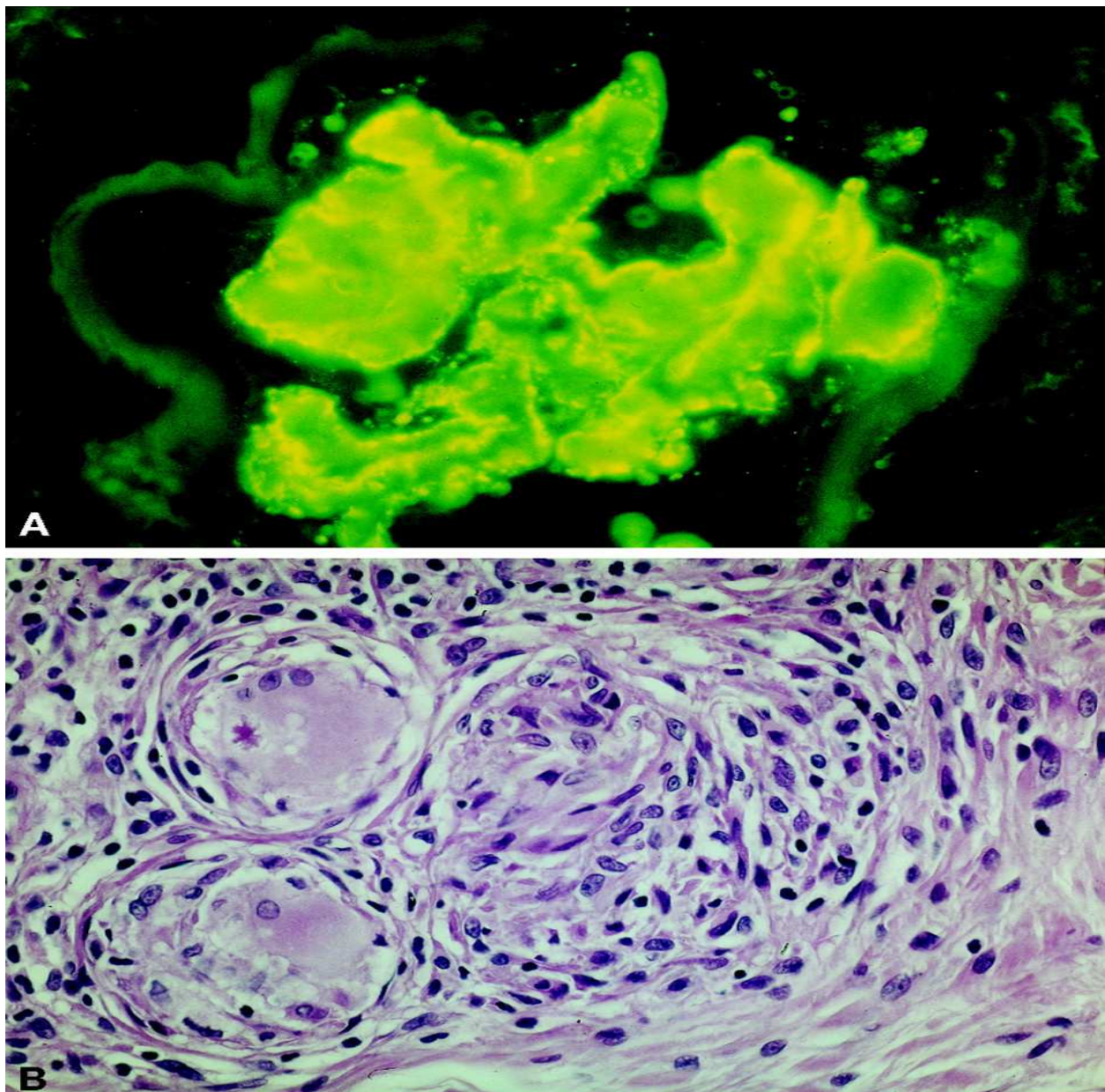


Fig. 2. (A) Immunofluorescence shows granular IgG deposits along the glomerular basement membrane consistent with membranous glomerulonephritis. (B) Left forearm biopsy with epithelioid granulomas. A star-shaped asteroid body is visible within a giant cell. Magnifications: x800 in A (IgG); x500 in B (hematoxylin and eosin). Gobel U et al. JASN 2001;12:616-623

## 5.2 Minimal change disease

Nephrotic syndrome due to minimal change disease (MCD) also has been described in patients with sarcoidosis. Mundlein et al, described a patient with Grave's disease with steroid dependent MCD who achieved complete remission with cyclophosphamide. (Mundlein et al 1996) Patient was subsequently diagnosed to have typical chest findings of pulmonary sarcoidosis. In contrast, Parry and Falk described a case of longstanding pulmonary sarcoidosis that later went on to develop steroid resistant MCD not responding



to high dose steroids or cyclophosphamide. (Parry et al 1997) The patient had to be started on cyclosporine which was given for a year and a sustained remission was attained. Spontaneous occurrence and remission of heavy proteinuria coinciding with the relapse of the disease is also well described. (Mery 2005) The authors postulated that there is a functional and transient increase of glomerular permeability to proteins secondary to release of vascular permeability factor like lymphokines by activated T cells.

### 5.3 Crescentic glomerulonephritis

Crescent Glomerulonephritis (GN) has also been frequently reported in patients with sarcoidosis and co-existing ANCA associated vasculitis. ANCA are autoantibodies found in some autoimmune diseases, recognized by their reactivity with cytoplasmic antigens in neutrophils; two groups are recognized: c-ANCA, reacting with proteinase 3, is found in polyangiitis and Churg-Strauss syndrome; p-ANCA, reacting with myeloperoxidase is found in Wegener granulomatosis. Auinger et al described a patient with rapidly progressive glomerulonephritis and hepatosplenomegaly with no prior diagnosis of sarcoidosis whose renal biopsy showed crescentic GN. (Auinger et al 1997) Diagnosis of sarcoidosis was made with raised angiotensin converting enzyme (ACE) levels and both liver and kidney biopsies showing interstitial noncaseating granulomas. Patient was started on high dose steroids with which renal function improved. Subsequently, the patient developed anti- myeloperoxidase (MPO) antibodies. In contrast, Ahuja et al reported a patient with crescentic GN in the setting of Wegener's granulomatosis (WG). (Ahuja et al 1996). Patient responded well to long term oral cyclophosphamide treatment. Subsequently, the patient developed biopsy-confirmed pulmonary sarcoidosis months later. Given such close associations, it is believed that these sarcoidosis and granulomatous vasculitis like WG may have some common mechanisms. See Figure 3.

### 5.4 Other glomerular diseases

Rare associations of sarcoidosis with post-infectious GN have also been noted. Michaels et al. described two patients with sarcoidosis : one with recent history of pneumonia and other with elevated antistreptolysin O titres who developed acute renal failure with active urinary sediments and nephrotic range proteinuria (Michaels et al 2000). Biopsies disclosed diffuse endocapillary proliferative GN with hump-like epithelial deposits. Both patients responded well to corticosteroids with resolution of proteinuria and azotemia. Similarly IgA nephropathy (IgAN), coexisting with sarcoidosis is not unusual given the wide prevalence of IgAN. Taylor and Nishiki described a case of IgAN in sarcoidosis typically presenting as nephritic syndrome that responded well to steroids. (Taylor et al 1996 and Nishiki et al 2010) Renal amyloidosis (AA type) has also noted in patients with long standing sarcoidosis with the classical presentation of steroid resistant nephrotic syndrome with slow progression to end stage renal disease. (Tchenio et al. 1996 and Rainfray et al 1988).

## 6. Tubulointerstitial diseases

After excluding abnormalities affecting calcium homeostasis, tubulointerstitial diseases are the most commonly encountered renal abnormalities in sarcoidosis. They are



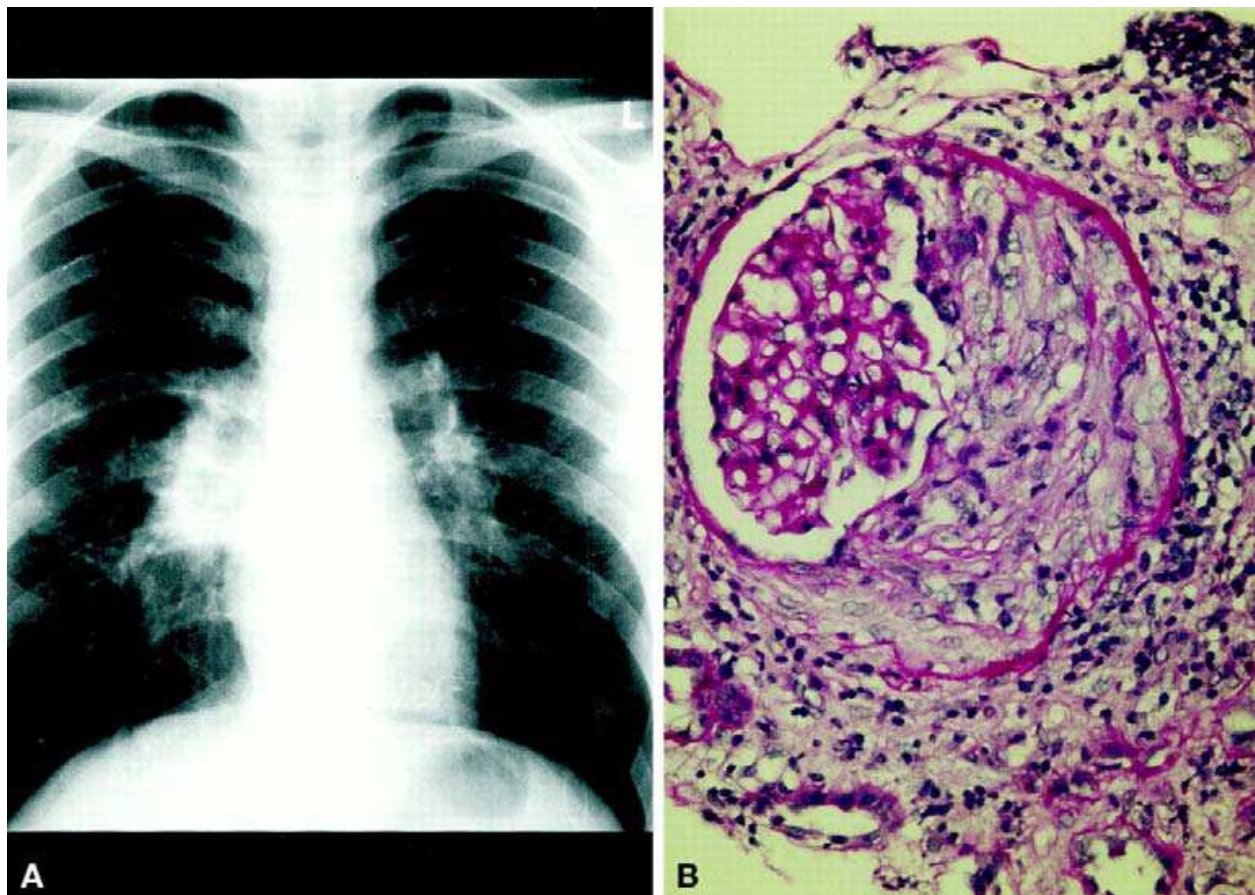


Fig. 3. (A) Roentgenogram showing bilateral hilar adenopathy in a patient with sarcoidosis. (B) Extracapillary glomerulonephritis with crescent formation. Magnification, x500 (periodic acid-Schiff). Gobel U et al. JASN 2001; 12:616-623

histopathologically described as granulomatous interstitial nephritis (GIN). Approximately 20% of patients with sarcoidosis show granulomatous inflammation in the kidney (Sheffield 1997) although values range from 15 to 40% (Mery 2005) reflecting differences in the indication for renal biopsies. In many instances, patients may be clinically silent and GIN may present with concomitant findings with well known clinicopathological syndromes. The variability in incidence of GIN also reflects sampling error in detecting scarce granulomas especially in inadequate biopsy specimens.

Overall GIN is a rare histologic diagnosis seen in 0.5 and 0.9% of native renal biopsies and 0.6% of renal transplant biopsies (Joss et al 2007). Possible etiologies include medications, infections, sarcoidosis, Sjogren's syndrome, crystal deposits, paraproteinemia, Wegener's granulomatosis and idiopathic causes. Drugs implicated include anticonvulsants, antibiotics, nonsteroidal anti-inflammatory drugs, allopurinol, and diuretics. Mycobacteria and fungi are the main infective causes and seem to be the main causative factor in cases in renal transplants or in countries with high prevalence of tuberculosis. In the largest collection of data so far on this disease, Joss et al noted 18 cases of GIN from etiologies such as sarcoidosis (n=5), drug induced (n=2), idiopathic (n=9) and tubulointerstitial nephritis with uveitis (n=2). The most common presentation of GIN was advanced renal failure with minimal proteinuria. (Joss 2007)

Despite great clinical variability, the most common clinical syndrome associated with sarcoidosis and GIN is chronic kidney disease with decline in renal function usually over weeks to months (Jean-Phillipe 2005). Acute renal failure as an initial presentation is also well known (O’Riordan et al 2001). Renal dysfunction may progress at variable rates but can irreversibly progress to end stage renal disease despite high dose glucocorticoid treatment. (Tsiouris et al 1999) Consistent with a pattern of tubulointerstitial disease, proteinuria is either absent or mild. Urine analysis shows leucocytes and granular casts. Rarely, patient may present as frank hematuria lasting several weeks. (Mills et al 1994) Functional tubular abnormalities can occur in as much as 50% of cases of sarcoidosis when aggressively investigated which include renal glycosuria, urinary sodium and potassium wasting, Fanconi’s Syndrome, decreased urinary concentration ability, proximal or distal tubular acidosis. (Muther et al 1981) It is uncertain whether the presence of interstitial lesions solely contributes to these abnormalities but hypercalcemia and hypergammaglobulinemia also play a pathogenic role. (Mery, 2005)

GIN is usually associated with enlarged kidneys mimicking polycystic kidney disease or renal carcinoma. (Mery, 2005) Renal sonogram shows bilateral renal masses which are either hyper- or hypoechoic in comparison to adjacent renal parenchyma. Computer tomogram shows the renal masses to be low intensity. A Gallium-76 citrate scan commonly reveals increased uptake suggesting active granulomatous inflammation. (Mery and Kenouch, 1988) Serum ACE concentration is a poor marker of active renal lesion and may even be normal in active GIN with severe renal failure. (Hannedouche et al 1990)

In most cases, a diagnosis of GIN is made in the context of typical extra-renal manifestations of sarcoidosis and/or hyperkalemia. Rarely renal involvement may be isolated and preceding other sites of the disease for months to years. Some have even considered isolated GIN as a localized form of sarcoidosis. In such isolated cases, it is important to rule out drug induced interstitial nephritis which is far more easily treatable cause of GIN than sarcoidosis itself. (Muther et al 1981) Another syndrome commonly associated with Sjogren’s Syndrome but also reported with sarcoidosis is the “TINU syndrome or the Dobrin Syndrome (Sinnamon et al 2008) which is characterized by acute interstitial nephritis, anterior uveitis and epithelioid granulomas in bone marrow and lymph nodes. The renal lesion consists of interstitial infiltrates mainly composed of mononuclear cells and few eosinophils. Although no interstitial granulomas are seen in TINU, the interstitial cell infiltrate is the same as a sarcoid granuloma. Therefore it is possible that some cases described as Dobrin syndrome may be atypical forms of sarcoidosis.

Analyzing all cases of GIN, Joss et al, noted that the background diagnosis of sarcoidosis was known in only 1 of 5 patients of GIN who eventually were categorized as sarcoid GIN. Mean age of presentation was 56. 8 years. ACE levels were elevated in a minority of patients (1 out of 5) and hypercalcemia was seen in only 2 patients. Pulmonary findings of hilar lymphadenopathy was seen in only 1 patient and one had the TINU syndrome.

(Joss et al 2007)

Renal pathology of GIN consists of the typical non-caseating granuloma widely distributed throughout the cortex and the medulla, although the density of these lesions may differ from patient to patient. (Mery 2005) The sarcoid granuloma consists of lymphocytes, mononuclear, cells and plasma cells. The center of the granuloma consists of epithelioid and



multinucleate giant cells both of which are derived from activated macrophages. Multinucleate giant cells are formed by the coalescence of epithelioid cells. Lymphocytes largely consist of T-helper cells (CD 4<sup>+</sup>) in the center and CD 8<sup>+</sup> lymphocytes in the periphery. Some granulomas have small arteries in their center. Although granulomas may also form in drug induced interstitial nephritis it is less well formed than in sarcoidosis. Varying degrees of fibrosis may also be present. The severity of fibrosis correlates with tubular atrophy and degeneration. In the absence of any predominant glomerular pathology, the glomeruli are either normal or show mesangial hypertrophy and thickening of the basement membrane. Electron microscopy may show fusion of epithelial foot processes (Farge et al 1986). However, there are no significant immune deposits in either the glomeruli or tubules as seen by immunofluorescent microscopy. In a significant number of cases, immunofluorescence with anti-ACE serum showed localization in the sarcoid granuloma in addition to normal staining of the brush border of the proximal tubules. (Mery et al 1988) See Figure 4.

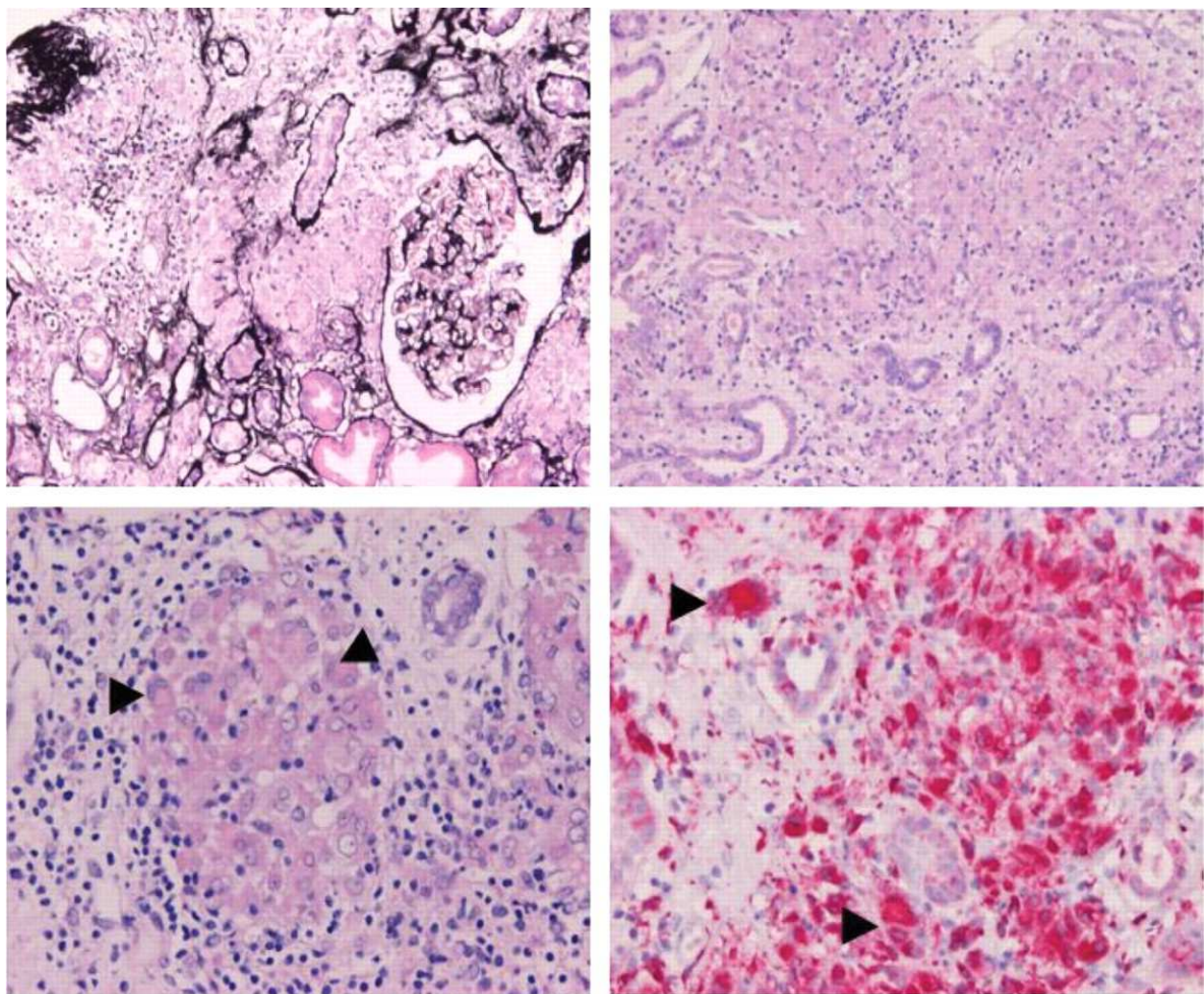


Fig. 4. Renal biopsy showed a granulomatous interstitial nephritis with a broadened interstitial, cellular infiltrates and granuloma with typical multinucleated giant cells (arrowheads). Kettritz R et al. *Nephrol. Dial. Transplant.* 2006; 21:2690-2694

In contrast to conventional pathological dogma, Joss et al showed that asteroid bodies and calcification were not common in sarcoid GIN. (Joss et al 2007) Interestingly, asteroid bodies were seen in 1 case of drug induced AIN. However, lymphocyte cuffing and giant cell infiltration were prominent in sarcoid granulomas in the kidney. Necrosis and eosinophil infiltration of the interstitium was more common in drug induced GIN as compared to sarcoidosis. It is now believed that idiopathic GIN, TINU and sarcoidosis represents a clinicopathological spectrum and that idiopathic GIN or TINU may subsequently develop typical extra-renal manifestations of sarcoidosis.

### 6.1 Treatment

The mainstay of treatment of sarcoid GIN is glucocorticoids. Initial treatment requires a daily dose of prednisone or prednisolone preferably 1-1.5 mg/kg. Response to treatment can often be dramatic in terms of improvement of renal insufficiency. The best response to glucocorticoids was noted in a study by Mahevas et al. in which 47 patients with renal sarcoid received prednisolone while 10 also received pulse methylprednisolone. (Mahevas et al 2009) The authors concluded that at 24 months, a complete and partial remission occurred in 30 and 5 patients respectively. But no response was noted in patients with severe interstitial fibrosis of greater than 50%. Underlying functional tubular dysfunction improves with progressive drop in serum creatinine. An important point to realize here is that steroid treatment has to be prolonged and must exceed at least 6 months as nephropathy relapses very frequently with short term therapy (Gene and Cheviot 1988). A commonly followed strategy is to give the initial dose for 2 months followed by progressive taper and switching to an alternate -day therapy. A maintenance therapy period for 1 year at least is recommended. Serial renal biopsies have shown a regression of granuloma in conjunction with improvement of renal function (Farge et al 1986) although given the variability in results (Gene and Cheviot 1988) routine biopsies after starting steroids is not recommended. Treatment in advanced disease is often associated with interstitial fibrosis along with focal segmental glomerulosclerosis and vascular lesions. However, vascular lesions are more common with long term corticosteroid therapy and are associated with delayed development of hypertension which is a major contributor to progression of renal failure. (Mery and Kenouch 1988)

While analyzing outcomes of steroid treatment in a heterogeneous population of GIN, Joss et al, presented data of 16 patients of which 5 were labeled as sarcoidosis. Patients were treated with prednisolone (starting dose of 0.55mg/kg) (Joss et al 2007) for a mean period of 25 months and then followed up for a period of 45 months. Overall, renal function stabilized or improved at the end of the study with mean GFR improving from 21 to 56 ml/min. One patient who was on dialysis at the beginning of therapy was able to discontinue dialysis within 3 months. Six patients relapsed on dose reduction of which 4 were sarcoid GIN who required azathioprine to break steroid dependence. Sarcoid patients required longer treatment (36 months) as compared to idiopathic or TINU patients. The greatest renal recovery occurred in the first year of treatment. There was no difference in renal outcome when analyzing the degree of interstitial fibrosis. Age less than 60 years was associated with a better outcome. Table 1 summarizes data on treatment of GIN in some important studies so far.

Long term results with steroid therapy in sarcoid GIN have not been rigorously tested in randomized controlled trials. In a large case series of 39 patients with sarcoid renal disease,



Parameter	Joss et al		Robson <i>et al.</i>	O’Riordan <i>et al.</i>	Hannedouche <i>et al.</i>	Brause <i>et al.</i>
<i>n</i>	18	16 <sup>1</sup>	7	5	6	5
Cause	Mixed	Idiopathic/ TINU/sarcoid	Idiopathic	Isolated sarcoid	Sarcoid	Sarcoid
Age (yr)	55	56	69	48 to 71	62	61
Male gender (%)	61	56	71	60	50	60
Renal function at baseline						
BaselineCC (ml/min)	21	24	14	6	NA	NA
Baseline creatinine (μmol/L)	373	357	420	NA	566	396
Hypercalcemia	3/18	3/16	2/7	0/5	2/6	1/5
Raised serum ACE	4/17	4/15	3/7	1/5	4/4	1/5
Improved renal function	17/18	15/16	5/7	4/5	6/6	5/5
Long-term RRT	0/18	0/16	2/7	0/5	0/6	0/5
Prednisolone (%)	89	88	100	100	100	100
Mean follow-up (mo)	45	48	25	35	75	NA
Renal function at last visit						
ECC (ml/min) at end of therapy	56	53	22	20	NA	NA
Creatinine (μmol/L) at end of study	159	159	296	NA	192	225

<sup>1</sup> Data excluding the two cases of drug-induced GIN.

Table 1. Comparison on treatment of GIN in literature.

17 patients with biopsy-proven tubulo-interstitial nephritis with significant renal impairment were analyzed over a one year period of corticosteroid therapy. (Robson et al 2003). All patients were initially started on prednisolone at 0. 5 mg/kg body weight at a daily dose of 30-60 mg which was tapered by 5 mg each week once the renal function has improved and/or stabilized. Thereafter, patients were maintained on 5-7. 5 mg daily indefinitely. Mean duration of study was 84 months. Estimated glomerular filtration rate (eGFR) at baseline was 26. 814 ml/min which improved to 49. 65. 2 ml/min (P<0. 01) at 1 year, and 47. 96. 8 ml/min (P<0. 05) at last review. Interestingly, the response to treatment was similar regardless of the degree of renal impairment at baseline, race and the degree of tubulo-interstitial scarring on renal biopsy. Three patients developed side effects that could

be attributed to steroids which included acute psychosis and type 2 diabetes. Long term use of corticosteroids, especially in adolescents, can cause substantial side effects including diabetes, growth retardation and cataract. Alternative agents that have been attempted in treating sarcoid GIN include mycophenolate (Moudgil 2002) and mizoribine (Rajakariar et al 2006 and Ito et al 2009) which are limited to case reports and have been primarily used in pediatric patients to break steroid dependence or ameliorate significant side effects. Other agents which have been tried in systemic extra-renal sarcoidosis include mycophenolate mofetil, methotrexate, azathioprine, antimalarials, and phosphodiesterase inhibitors such as pentoxifylline and thalidomide although no data on treating renal sarcoidosis exists. (Baughman 2003) There has been great interest in the use of TNF-antagonists as another modality to treat sarcoid GIN in order to avoid use of steroids. TNF-alpha, which is expressed by monocytes, is critical in the development of these noncaseating granulomas. TNF-alpha receptor antagonists have also been shown to prevent the initiation and perpetuation of inflammation and subsequent interstitial fibrosis. Etanercept is a soluble TNF-alpha receptor fusion protein that binds TNF-alpha. Infliximab and adalimumab are monoclonal antibodies that bind specifically to and neutralize TNF-alpha. While etanercept is an ineffective agent in the treatment of systemic sarcoidosis, (Ulz et al 2003) infliximab has been shown to be effective in a case of renal sarcoid. Thumfart et al, described the case of a boy presenting with severe arterial hypertension and acute renal failure caused by an isolated sarcoid granulomatous interstitial nephritis. Renal function improved initially with prednisone treatment but later, the patient showed signs of severe steroid toxicity and progressive renal failure. Monthly treatment with infliximab was initiated resulting in a steady improvement in renal function and resolution of renal granulomata, as well as reduction in antihypertensive medication. (Thumfart 2005) Ahmed et al presented a patient with acute renal failure due to isolated granulomatous infiltration of the renal parenchyma. (Ahmed et al 2007) Renal biopsy showed granulomatous interstitial nephritis with noncaseating granulomas. There was no evidence of extrarenal sarcoid involvement. Prednisone 60mg daily resulted in significant improvement in renal function. Due to recurrent flares while tapering the prednisone and steroid toxicity, treatment with infliximab was instituted and resulted in stabilization of renal function. This case demonstrated that steroid-dependant or refractory renal sarcoidosis cases may respond to infliximab. We recently reported the case of a 46-year-old woman with multi-organ sarcoidosis, type 2 diabetes, subnephrotic-range proteinuria, hypertension and recurrent episodes of hypercalcemia-induced acute kidney injury who was referred for evaluation of worsening renal function and nephrotic range proteinuria. (Gupta et al 2008) A kidney biopsy showed sarcoid GIN with moderate-to-severe chronic tubulointerstitial disease, hypertensive vasculopathy, and diabetic glomerulosclerosis. Because steroids had caused multiple side effects including diabetes, hypertension and obesity and attempts to wean steroids had caused hypercalcemia and acute renal failure, Adalimumab (Humira™) 40 mg/0.8 cc weekly for 6 months was initiated. After 6 months of treatment with adalimumab, serum creatinine improved from 345  $\mu\text{mol/L}$  (3.9 mg/dL) to 1.8 mg/dl (her baseline for years) and proteinuria improved from 10 g/day to 3.5 g in 24 hours respectively. A repeat biopsy showed persistent diabetic glomerulosclerosis, moderate chronic tubulointerstitial inflammation with complete resolution of interstitial epithelioid granulomas. Although adalimumab and infliximab are generally safe, some side effects

include risk of lymphoma and reactivation of latent tuberculosis (Denys et al 2007). These agents may hold promise for the future once large scale randomized studies are available to show consistent benefits with minimal side effects.

## 7. Renovascular diseases associated with sarcoidosis

Renovascular diseases secondary to sarcoidosis are distinctly rare and attributed to a form of secondary vasculitides. Systemic vasculitis associated with sarcoidosis has been reported as an isolated entity in the literature after excluding other common causes of vasculitis. It is predominantly large vessel vasculitis although few instances of small vessel vasculitis have been reported. In a large case series and review of literature on sarcoid vasculitis, Fernandes et al, noted that most cases were children and clinical presentation resembled hypersensitivity vasculitis, Takayasu's arteritis, polyarteritis nodosa or microscopic polyangitis. (Fernandes 2000) Clinical features included fever, peripheral adenopathy, hilar adenopathy, rash, pulmonary parenchymal disease, musculoskeletal symptoms, and scleritis or iridocyclitis with biopsy showing necrotizing sarcoid granulomata. Interestingly, no renal involvement was noted. Notably the authors found large vessel vasculitis largely in the African American population while small vessel vasculitis predominantly affected white races. Godin et al described a known case of pulmonary sarcoidosis with persistent hypertension. (Godin et al 1980) Diagnostic evaluation for renovascular hypertension included aortography which showed severe stenosis of right renal artery. Surgical exploration showed extensive periaortic and perirenal fibrosis with extrinsic compression of renal artery. Pathological examination of the kidney revealed epithelioid infiltration of the adventitia of renal artery suggestive of sarcoid angitis. Surgical biopsy was performed on both kidneys. The right kidney, protected by arterial stenosis, was slightly altered, while the left kidney showed extensive interstitial, tubular, and glomerular lesions which included focal and segmental hyalinosis. Marcussen et al, reported an autopsy case of a middle aged man who died of myocardial infarction secondary to fulminant vasculitis. (Marcussen and Lund 1989) Pathology showed widespread giant cell vasculitis with simultaneous involvement of the renal arteries, veins, and arterioles along with typical interstitial sarcoid granuloma. Shintaku et al, showed granulomatous inflammation of small renal vessels and crescentic GN on the autopsy of a patient with pulmonary hemorrhage and rapidly progressive renal failure. (Shintaku et al 1989) Thus, sarcoid angitis, especially causing small vessel vasculitis in the kidney may represent a very severe form of sarcoidosis. In their review, Fernandes et al, noted that four out of six patients responded well to steroid treatment alone but had relapses when attempts were made to taper or withdraw steroids. (Fernandes 2000) Frequently, there is an overlap between sarcoidosis and well known causes of granulomatous vasculitis. For instance, Watson et al described a case of longstanding pulmonary sarcoidosis presenting with rapidly progressive renal failure with p-ANCA positivity. (Watson 1996) Renal biopsy demonstrated focal and segmental fibrinoid necrosis with crescentic GN and focal fibrinoid necrosis in arterial wall, but no granulomata and pauci-immune deposits on immunofluorescence. Unlike patients with ANCA positive vasculitis, the index case responded poorly to pulse steroids and cyclophosphamide and progressed rapidly to end stage renal disease.

## 8. Kidney transplantation in patients with sarcoidosis

The usual cause of end stage renal disease in sarcoidosis requiring renal replacement therapy is usually due to hypercalcemic nephropathy rather than granulomatous interstitial nephritis or a glomerular disease. The outcome in renal transplantation in patients with sarcoidosis has been described in the literature. The first recurrence of sarcoid GIN in renal allograft was diagnosed 6 years after deceased donor kidney transplantation in a patient that was diagnosed with GIN before transplantation (Shen et al 1986). A recent French study aimed to describe a multicenter experience with kidney transplantation in patients with sarcoidosis. (Aouizerate et al 2010) In this study, the authors retrospectively identified 18 patients who underwent renal transplantation. Patient medical charts, demographics were reviewed. The median time between the last sarcoidosis episode and renal transplantation was 78 (8 to 900) months. Only 3 out of 18 patients had been on immunosuppression prior to transplantation. Vast majority of the patients had in the past received steroids and other immunosuppression for their sarcoid before transplantation. Renal disease was attributable to biopsy proven renal sarcoid in 10 out of the 18 patients and was attributed to other causes in 8 patients. Mean age of transplantation was 43. 5 +/- 11 years. 17 out of 18 patients had a deceased donor transplant. Mean donor age was 36. 5 +/- 15 years. Mean cold ischemia time was 16. 6 +/- 8 hours. 11 patients received induction therapy with anti-thymocyte globulin or Il-2 receptor antagonists. Maintenance immunosuppression included calcineurin inhibitor (CNI) for all patients, mycophenolate mofetil or azathioprine, sirolimus and corticosteroids for 16 out of the 18 patients. At the end of the 42 month follow up period, patient and death censored graft survival was 94. 4% and mean GFR was 60 cc/min per 1. 73 m<sup>2</sup>. Recurrence of sarcoidosis after renal transplantation was observed in 5 (27%) of patients. The median period between renal transplantation and recurrence was 13 months and four of five patients exhibited recurrence in the first 18 months after renal transplantation. Recurrences involved in the same organ in four of five patients and included renal involvement in three patients and lung and liver involvement in one patient. Mean GFR at end of follow-up was significantly lower in the three patients with recurrence than that for the entire cohort. (31 versus 60 cc/min per 1. 73 m<sup>2</sup>). Analysis of the recurrences showed that they occur in the first 18 months after transplantation. Primary disease related to sarcoidosis was strongly associated with recurrence (40% in the group with renal sarcoidosis versus 12. 5% in a group with a primary nephropathy, and median period between last episode of sarcoidosis and renal transplantation was shorter in the case of sarcoidosis recurrence (42 versus 78 months respectively). This study showed that patients with initial renal involvement display sensitivity to disease recurrence in allograft. The incidence of recurrence was significant as all patients were maintained on triple immunosuppressive therapy including steroids and mycophenolate mofetil. This study showed that renal transplant can be conducted safely in transplant patients with sarcoidosis, but recurrences do occur and affect overall graft outcome.

Kukura reported a case of recurrence of sarcoidosis in the renal allograft during pregnancy. (Kukura et al 2004) This was a 27 yr old female diagnosed with sarcoidosis at age 14 by lacrimal and parotid gland biopsy. 4 years after presentation, she developed hypertension and renal insufficiency. Kidney biopsy showed interstitial nephritis and nephrosclerosis, but no granulomas. Patient was eventually started in hemodialysis and underwent kidney



transplantation with excellent graft function with a creatinine of 1.32 mg/dl and a negative urinalysis. Patient was maintained on cyclosporine, azathioprine and prednisone 25 mg by mouth daily. 2 years after transplantation once the steroids were withdrawn, patient continued to have good kidney function with an allograft biopsy showing mild chronic allograft nephropathy only. Immunosuppression consisted of azathioprine and cyclosporine. At 3 years after kidney transplantation, patient became pregnant. 29 weeks into pregnancy, renal function worsened. Biopsy showed numerous noncaseating granulomas bound to the arteries, initial arteritis in one artery, mild interstitial mononuclear inflammation and tubulitis. Graft function improved with pulse methylprednisolone and tapered steroids were used. After delivery, renal allograft biopsy was performed 6 months which showed baseline disease of mild chronic allograft nephropathy and sporadic granulomas. This case demonstrates that steroid withdrawal after kidney transplantation may lead to sarcoidosis recurrence.

The implication that sarcoid reflects a disease phenomena related to the immunologic stimulus makes sarcoidosis an unlikely diagnosis to be made in an immunosuppressed patient such as an organ transplant recipient. However, Schmidt et al showed that after kidney transplantation, sarcoidosis can occur in the lung and pleura. (Schmidt et al 1999) In this case, a 41 yr old with history of IgA nephropathy and no past medical history received a living related kidney transplant and had been receiving tacrolimus therapy. He was found to have a large pleural effusion 17 months after kidney transplant. Diagnosis of sarcoidosis was established by identifying noncaseating granulomas, some with multinucleated giant cells in the pleural and lung tissue. All viral and bacterial workup was negative. The effusion resolved after initiating corticosteroid therapy. One month into therapy, the effusion resolved and patient continued to be asymptomatic twenty months after therapy. The authors did not speculate on the pathogenesis of granuloma formation since both tacrolimus and corticosteroids interfere with T lymphocyte function and granuloma formation. They speculated that activation of tissue chemokines of the IP-10 type during the posttransplant period, along with subsequent recruitment of lymphocytes and macrophages may have resulted in the sarcoidosis.

## 9. Conclusion

Sarcoidosis is a disease that primarily affects the reticuloendothelial system but can affect all tissues and organ systems. In this chapter, we described the effects of sarcoidosis on the kidneys. This disease affects patients worldwide and is defined pathologically by the presence of noncaseating granulomas in the involved tissue. The etiology of sarcoidosis has yet to be determined but some have proposed a possible infectious etiology. Commonly sarcoid patients present with hypercalcemia, hypercalcuria, and nephrolithiasis due to the overproduction of calcitriol from the epithelioid granulomas. We also described the rare glomerular and renovascular manifestations of sarcoidosis. Granulomatous interstitial nephritis is most commonly associated with sarcoidosis. It is a histological diagnosis and can be treated with both steroids and TNF-alpha antagonists. Kidney transplantation is safe in patients with sarcoidosis but we must keep in mind the disease can recur in the allograft. In conclusion, sarcoidosis is a complex disease and presents both a diagnostic and management challenge to the physician.

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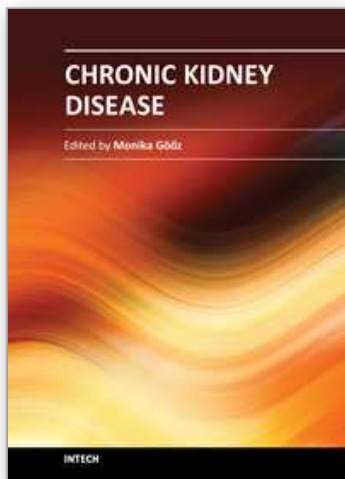
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Chronic kidney disease is an increasing health and economical problem in our world. Obesity and diabetes mellitus, the two most common cause of CKD, are becoming epidemic in our societies. Education on healthy lifestyle and diet is becoming more and more important for reducing the number of type 2 diabetics and patients with hypertension. Education of our patients is also crucial for successful maintenance therapy. There are, however, certain other factors leading to CKD, for instance the genetic predisposition in the case of polycystic kidney disease or type 1 diabetes, where education alone is not enough.

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