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ISOLATED RENAL SARCOIDOSIS WITH ACUTE KIDNEY INJURY - A RARE ENTITY

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ABSTRACT

Sarcoidosis is a multisystem inflammatory disorder that commonly affecting the lungs. However, isolated renal sarcoidosis without lung involvement is a rare condition. Sarcoidosis is known to cause kidney involvement via different mechanisms. Hypercalcemia and hypercalciuria may trigger renal stones formation and result in obstructive uropathy. Sarcoidosis can also cause interstitial nephritis with or without granuloma formation in the kidneys. The true incidence of renal involvement in sarcoidosis is unknown as renal biopsy is not routinely performed unless there is presence of renal impairment. Renal sarcoidosis is a diagnosis of exclusion supported by the typical histopathological findings. Due to the scarcity of this disease, there is no universal guideline or recommendation regarding the diagnosis and treatment for renal sarcoidosis. Here we present a case that initially presented to us with rapid deterioration of kidney function, which was later proven to be renal sarcoidosis, followed by a literature review.

Keywords : renal, sarcoidosis, literature review

INTRODUCTION

Sarcoidosis is an inflammatory disease of unknown aetiology characterized by intense cell-mediated immune reaction and granuloma formation. It is often diagnosed by clinical manifestations and radiographic features, with the presence of non-caseating granuloma. It is a multisystem disorder that mainly involves lung in more than 90% of the cases. However, it may also affect the heart, skin, eyes, kidney, and central nervous system (1). Isolated renal sarcoidosis is rare, and renal involvement can be initiated via multiple pathways, which include hypercalcemia and/or hypercalciuria, granulomatous interstitial nephritis, glomerulopathy, tubular dysfunction, as well as obstructive and vascular uropathy (2). A retrospective study done by Javaud el al showed that granulomatous interstitial nephritis appeared to be the most common renal manifestation in sarcoidosis (3). Corticosteroids remain the cornerstone of treatment, especially with the presence of granulomatous interstitial nephritis, and most patients have excellent treatment responses, although the rate of relapse is high. Nevertheless, due to the scarcity of this illness, there is no standardized protocol regarding the optimal dose and the duration of therapy (2).

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CASE REPORT

A 37 years old gentleman was referred from his primary care physician with acute kidney injury. He initially presented with easy fatigue and reduced effort tolerance for the past two weeks. He denied any chest pain, orthopnoea, paroxysmal nocturnal dyspnoea, leg swelling, polyuria, polydipsia, or abdominal pain. He had no medical illness, and none of the family members had similar symptoms or kidney disease. He gave a history of taking traditional herbs in an attempt to alleviate the symptoms but stopped after 3 days. He denied taking alcohol, tobacco, or illicit drugs. He worked as a machine cleaner where he routinely cleaned dust, dirt, grease from the factory machines. When he first presented to his primary care physician, he was diagnosed to have hypertension and was started on losartan/hydrochlorothiazide 50/12.5 mg once daily.

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He was also detected to have renal impairment and was referred to nephrology clinic urgently for further workup and treatment.

During the nephrology consultation, his blood pressure was 121/77mmHg with unremarkable physical examination. Serum creatinine was 374 µmol/L with normal full blood count and fasting blood sugar. There was no eosinophilia in the peripheral blood film. CRP and ESR were normal (2.7mg/L and 13mm/hour). Serum calcium and phosphate levels were 2.22 mmol/L and 1.13mmol/L, respectively. Urine full examination and microscopic examination (UFEME) showed blood 1+ and protein 2+. Hepatitis B/C and HIV screening were negative. Chest radiography showed mild cardiomegaly. There was no perihilar lymphadenopathy seen.

He was admitted immediately for renal biopsy. At the same time, IV methylprednisolone 500mg daily for three days was given as there was high index of suspicion of rapidly progressive glomerulonephritis due to rapid deterioration of renal function with the presence of protein and blood in the urine. Prednisolone was started at 1mg/kg after completion of methylprednisolone. Losartan/hydrochlorothiazide was stopped due to the worsening of kidney function and replaced by amlodipine for blood pressure control. Throughout his stay in the hospital, his serum creatinine level significantly improved from the highest level of 596µmol/L to 429µmol/L after two days and 326µmol/L after one week. His urine protein/creatinine index came back few days later and only showed 0.02g/mmol. His serum C3/C4 level subsequently came back as normal. Antinuclear antibody (ANA), serum p-ANCA and c-ANCA were negative. The serum angiotensin-converting enzyme was 37 U/L (Normal range 16-85 U/L). 24 hours urine calcium was not sent as part of the initial workup because hydrochlorothiazide might affect the result and prednisolone was already initiated.

His renal biopsy showed two cores of renal corticomedullary tissues with a total of 25 glomeruli in a plane of section. Six glomeruli showed global sclerosis and three glomeruli showed segmental sclerosis with glomerular basement membrane wrinkling and periglomerular fibrosis. No glomerular fibrinoid necrosis, membrane thickening,

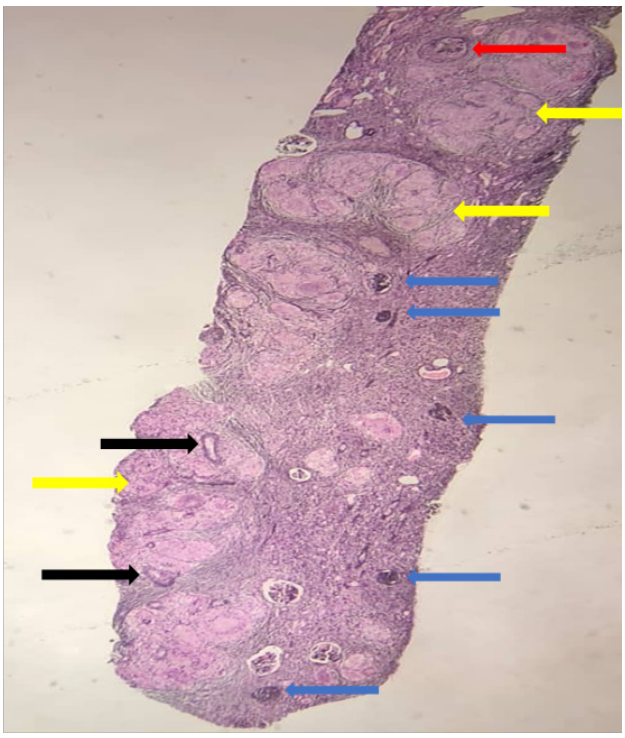

Figure 1: Total of 25 glomeruli identified, six glomeruli show global sclerosis (blue arrow) and three glomeruli shows segmental sclerosis (red arrow). The section also shows granulomas (yellow arrow), thickened vascular channels (black arrow) and a moderate amount of interstitial inflammation, PAAG: 40x.

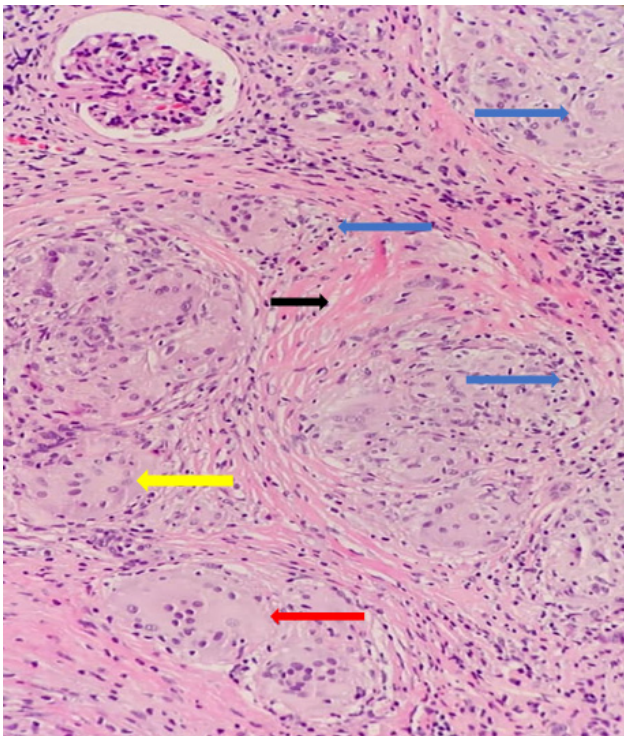

Figure 2: The granulomas are composed of aggregates of epitheloid histiocytes (blue arrow) with the presence of numerous foreign body type (red arrow) and touton type (yellow arrow) multinucleated giant cells. No central necrosis was seen. The surrounding interstitium shows fibrosis (black arrow), and moderate amount of inflammatory cells infiltrate, H&E: 100x.

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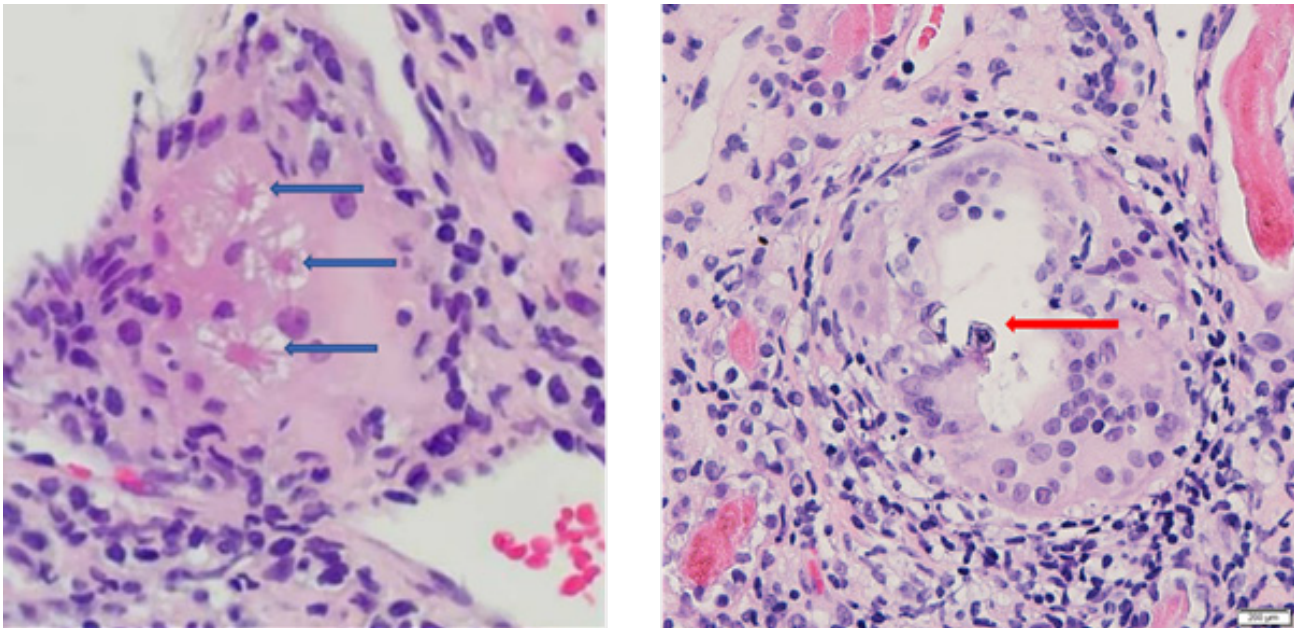

Figure 3: Picture at the left shows Asteroid bodies seen within the granulomas (blue arrow), H&E: 400x. The picture at the right shows single Schaumann like body within the granulomas (red arrow), H&E: 400x.

crescent, or endocapillary proliferation was seen. There were numerous granulomas seen within the cortex and medullary interstitium (figure 1). The granuloma was composed of aggregates of epitheloid histiocytes with the presence of numerous foreign body type and touton type multinucleated giant cells (figure 2).

Occasional Asteroid bodies and Schaumann like body were also noted (figure 3). No central necrosis was noted. The granulomas were predominantly seen surrounding medium and large-sized vascular channels. The vascular channels showed thickened, and hyalinized walls with occasional foci of mild lymphocytic infiltrate within the wall and reactive endothelial lining. The surrounding interstitium of the cortex and medullary region showed dense inflammatory cells infiltrate, composed of histiocytes, lymphocytes, plasma cells, occasional eosinophils, and rare neutrophils. There were focal areas with interstitial fibrosis. The tubules within the cortex were mostly lost, replaced by dense interstitial inflammation and fibrosis. Patchy areas within the cortex and medullary region showed the presence of dilated tubules, lined by reactive epithelium with the presence of occasional mitotic figures. The rest of the tubules within the medulla showed the presence of hyaline and occasional granular cast (figure 4). The lobular and interlobular vessels walls were thickened and hyalinized with occasional foci of mild lymphocyte infiltrate within the wall with reactive endothelial lining, surrounded by aggregates of epitheloid granuloma. No vascular wall fibrinoid necrosis was seen. Immunoperoxidase staining showed a negative result for IgG, IgA, IgM, C3, and C1q. PAS, PAAG, and GMS stains showed the existence of spherical bodies within the granuloma and interstitium. No acid-fast bacilli were seen with Ziehl-Neelsen stain. The morphology is in favour of

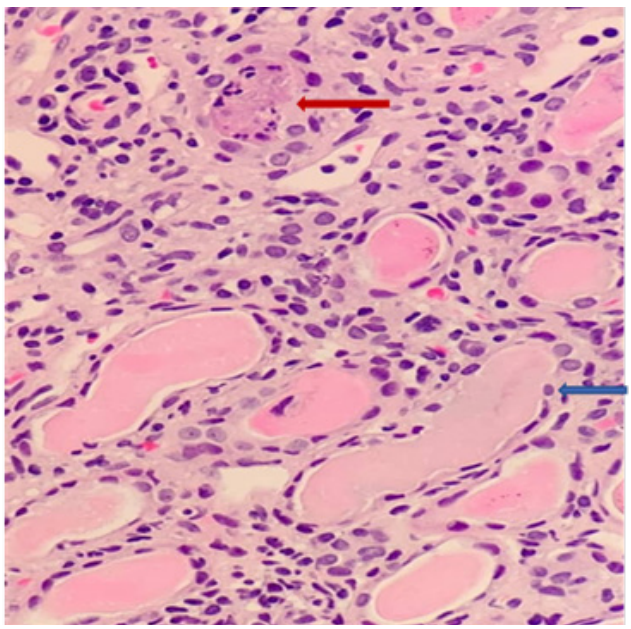

Figure 4: Some tubules show dilatation, lined by flattened epithelium, containing hyaline material (blue arrow) and granular cast (red arrow), H&E: 100x.

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renal sarcoidosis with concurrent acute tubulointerstitial nephritis and hypertensive vasculopathy. He was treated as isolated renal sarcoidosis based on the serology and renal biopsy results even though his serum calcium level was normal as hypercalcemia only presents in up to 34% of confirmed case of sarcoidosis. He did have history of taking traditional herbs, but drug induced granulomatous interstitial nephritis was less likely the diagnosis as his symptoms started prior to the herbal medication. He was discharged well after one week of stay in the hospital. During his monthly follow up in the nephrology clinic, his creatinine level remained stable at 256-258μmol/L. He is currently on a tapering dose of steroids.

DATA EXTRACTION

We carried out a limited qualitative systemic literature review of articles related to renal sarcoidosis from Pubmed, Google scholar, Springer Link and Science Direct. The Scopus index was used to verify the scientific relevance of the papers. Keywords used to search the studies are: 'sarcoidosis', 'renal sarcoid', 'granulomatous interstitial nephritis', 'sarcoidosis interstitial nephritis'. We have included studies that were published in English from years 2007 onwards and excluded those in abstract format only. Case reports or literatures reviews that were published as full articles were included.

DISCUSSION

Sarcoidosis is a multisystem disorder capable of affecting any organ in the body. Though the lung is the most commonly affected organ, screening for potential extrapulmonary involvement should be done in sarcoidosis. Isolated renal sarcoidosis is an uncommon but a well-accepted entity (4-5). Among those with renal sarcoidosis, acute kidney injury occurred in 0.7 to 4.3% of the patients. Out of this, 4 to 10% might develop end-stage kidney disease (ESKD) requiring long term renal replacement therapy (6).

The causes of renal impairment are multifactorial and are thought to include acute interstitial nephritis, obstructive uropathy secondary to nephrolithiasis, retroperitoneal lymph node or retroperitoneal fibrosis, or rarely due to glomerulonephritis (2,6). Interstitial nephritis with or without granuloma remained the most common renal manifestation of sarcoidosis (2,6-7). Mahévas et al. reported that out of 47 cases with biopsy-proven renal involvement of sarcoidosis, 78.7% of the biopsy sample were noted to have non-caseating granulomatous interstitial nephritis (7). The key features of the pathological process in granuloma formation may be due to the immune paradox, which related to the disequilibrium between effector and regulatory lymphocytes, which results in T cells gathering at the disease site. The centre of the granuloma is hypothesized to have poorly degraded antigen, surrounded by macrophages that will subsequently form multinucleated giant cells, with CD4+ helper cells interspersed within it, and CD8+ T cells, regulatory T cells, fibroblasts, and B cells surrounding the periphery (8). Renal sarcoidosis is a diagnosis of exclusion thus when granulomatous interstitial nephritis is identified in renal biopsy other causes need to be ruled out. Wegener granulomatosis, infection such as tuberculosis and fungal infection, TINU syndrome, antibiotics such as penicillin and cephalosporins, anti-inflammatory agents such as ibuprofen, and even post intestinal bypass have been reported to induce granulomatous changes in the kidney (3-4,9). Idiopathic granulomatous interstitial nephritis (GIN) will be the last diagnosis; however, there were several cases reports where the diagnosis of GIN lead to a subsequent diagnosis of sarcoidosis. Thus, it is possible that some cases of idiopathic GIN may represent unrecognized renal limited sarcoidosis (10).

As a result of the overproduction of vitamin D secondary to increased expression of 1-alpha-hydroxylase, hypercalcemia is also one of the common manifestations of sarcoidosis (2,6). Hypercalcemia is reported in 10-34% of patients with sarcoidosis (2,7). The increased vitamin D level causes suppression of parathyroid hormone, which indirectly induces increased renal excretion of the calcium causing hypercalciuria. Hypercalcemia and hypercalciuria lead to nephrocalcinosis and obstructive uropathy due to stone formation. They also induce acute tubular necrosis due to increased intracellular calcium and tubular obstruction secondary to calcium precipitate (2,11). Nephrolithiasis has been detected in 10-13.8% of the patients with the disease (12).

Urinary abnormalities such as proteinuria, microscopic haematuria, and leukocyturia may be present but the absence of these of markers does not exclude renal sarcoidosis (7). Other rare renal presentations of sarcoidosis include glomerular involvement (which can manifest as Ig A nephropathy, membranous nephropathy, focal segmental sclerosis, crescentic glomerulonephritis) and AA amyloidosis (2,11). Renal tubular dysfunction may present as a result of hypercalcemia and interstitial nephritis. Proximal or distal renal tubular acidosis, nephrogenic diabetic insipidus, metabolic alkalosis, or urinary concentration deficits have been reported in various case reports (2,12).

Sarcoidosis is usually a diagnosis of exclusion. Most of the time, the initial presentation is non-specific and vague. The patient can present with fever, fatigue, arthralgia, weight loss, and incidental findings of hypercalcemia and

deranged renal function during routine blood investigations (3-5,7). In the presence of appropriate clinical settings, non-necrotizing granuloma in the tissue sample without the evidence of infection is the usual diagnosis criterion. To establish the diagnosis of renal sarcoidosis, baseline renal function, urinary protein quantification, and calcium excretion as well as serum calcium level should be carried out. Ultrasound kidney should be done especially in patient with elevated serum calcium and urinary calcium excretion as nephrolithiasis or nephrocalcinosis is common (11). Ultrasound examination of the kidneys has sensitivity values of 85-90% to diagnose nephrocalcinosis; hence is the preferred modality compared to abdominal X-ray (12). Angiotensin-converting enzyme (ACE) level may be helpful but is not diagnostic as it is only elevated in 50-57% of cases (6,13). Renal biopsy should be attempted to establish the histopathological diagnosis of renal sarcoidosis, although the absence of characteristic kidney findings does not exclude the diagnosis (14). Interstitial inflammatory cell infiltration with granuloma formation is the most common finding in renal biopsy. Other findings may include glomeruli with focal ischemic tuft retractions, interstitial fibrosis, and tubulointerstitial microcalcifications (6,13,15). A variety of inclusion bodies may be found, which include Asteroid bodies, Schaumann bodies, birefringent crystals, and Hamazaki-Wesenberg bodies (13). These inclusion bodies are neither specific nor diagnostic for sarcoidosis as these can also be found in other granulomatous diseases like tuberculosis. Asteroid bodies are stellate inclusions with numerous rays radiating from a central core, which are being reported in 2-7% of sarcoidosis. Schaumann bodies are large concentric calcifications that form within the cytoplasm of giant cells and being reported in up to 88% of cases (15). Since pulmonary involvement is the commonest manifestation in sarcoidosis, once granulomatous interstitial nephritis is detected on renal biopsy, chest radiography and/or computed tomography (CT) of the chest should be done to evaluate for pulmonary sarcoidosis (1).

Treatment of renal sarcoidosis is focused on the management of hypercalcemia as well as interstitial nephritis (2). Patients with hypercalcemia may present with polyuria and polydipsia due to antidiuretic hormone insensitivity. Thus, the initial treatment of hypercalcemia will be to discontinue any calcium and vitamin D supplementation therapy and provide adequate hydration. A single dose of bisphosphonate could be administered at the same time. Loop diuretics to match hydration will further enhance the urinary excretion of calcium if calcium level remained high after adequate fluids administration (16,17). Glucocorticoids remain the recommended initial treatment as it suppresses the activity of 1-alpha hydroxylase, thus reducing the synthesis of vitamin D. To treat hypercalcemia in sarcoidosis, prednisolone has been recommended to be initiated at a dose of 0.3-0.5mg/kg/day (2). Alternative treatments include hydroxychloroquine and ketoconazole. Both drugs demonstrate the capacity of inhibiting the conversion of 25-hydroxyvitamin D to 1,25-dihydroxy vitamin D. The suggested dose of hydroxychloroquine is 200-400mg/day whereas for ketoconazole is 200-800mg/day (2,17). In addition, dietary intake of calcium should be lowered and reduced exposure to sunlight may provide additional benefits (16).

In the presence of interstitial nephritis, especially the granulomatous type, glucocorticoids remain the most effective treatment at the moment (2,11,17). Intravenous pulse methylprednisolone 500mg-1000mg daily for three days may be given if there is evidence of major organ impairment (2). The recommended starting dose of oral prednisolone is 0.5-1.0mg/kg, and it should be maintained for at least four weeks before tapering down to allow renal function stabilization (2,17). Those who have a poor response to the prednisolone after four weeks of treatment tend to have a poorer renal outcome (2). In the milder form of the disease, prednisolone can be started at 0.5mg/kg once daily (2,17). Prednisolone should be tapered down slowly (e.g. 5mg/week) and maintained at 5-10mg for at least 6-12 months before stopping treatment (2,11). Nevertheless, there were studies that suggested prolonging the treatment duration up to a total of 24 months in view of the high relapse rate especially when the prednisolone is being withdrawn (2). Due to the known adverse effects of prolonged glucocorticoid treatment, initiation of steroid-sparing agents like azathioprine and methotrexate as maintenance therapy have also been suggested (2,11,17). The dose of azathioprine is proposed at 2mg/kg/day (maximum 200mg/day) (17). Methotrexate with folic acid supplementation is another second-line treatment, with extra caution in use, especially in women of childbearing age since it is teratogenic. The recommended dose of methotrexate is 10-20mg/week (2,11,17). There is a higher probability of methotrexate toxicity in those patients with eGFR<50ml/min as this drug is renally excreted (7). Mycophenolate mofetil is another possible treatment option, at a suggested dose of 1000mg twice daily (2,17). Infliximab, a TNF-alpha inhibitor, has been used in several case studies related to steroid-resistant sarcoidosis. It is usually given in a dose of 3–5 mg per kg at week 0, 2, and 6 followed by every 6–8 weeks thereafter (2,17). Another biologic agent i.e. adalimumab is a potential treatment option but further studies are needed to prove its efficacy (2).

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The prognosis of renal sarcoidosis depends on age, race, the initial response to steroids, and the number of organ involvement. Elderly, African ethnicity, failure of response to steroids, extensive multiorgan involvement, and evidence of kidney scarring are poor prognostic indicators. ESKD is rare but if occurs, is usually due to hypercalcaemic nephropathy rather than granulomatous nephritis or glomerulonephritis (18). A large retrospective observational study consisting of 47 patients with sarcoidosis-related interstitial nephritis showed that only two patients developed ESKD requiring life-long renal replacement therapy (7). However, in the absence of steroid treatment, the decline from baseline renal function (with normal calcium levels) to ESKD (with hypercalcaemia) was seen in approximately two years (19).

There is paucity of literature regarding renal transplantation in sarcoidosis as the percentage of ESKD is low. Interestingly, a retrospective study done by French renal transplant department showed excellent patient and graft survival (94.4% of patients diagnosed with sarcoidosis) after median 42 months of follow up. Nevertheless, 27% of the patients had a relapse, and the disease recurrence occurred at a median period of 13 months. Risk factors for recurrence included primary renal disease related to sarcoidosis and a shorter delay between the last episode of sarcoidosis and renal transplantation. The authors concluded that renal transplantation may be carried out safely in transplant candidates with sarcoidosis (20).

CONCLUSION

Isolated renal sarcoidosis with acute kidney injury as an initial presentation is rare. Renal biopsy to establish the diagnosis is essential, and other diseases that can cause renal granulomatous inflammation must be ruled out. Prompt treatment is needed to avoid irreversible damage to the kidneys. Further studies are required to standardize the treatment protocol for renal sarcoidosis.

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