Sarcoidosis induced interstitial nephritis. A case series with literature review

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Abstract

Sarcoidosis is an idiopathic granulomatous disease with organ dependent unpredictable prognosis. Renal dysfunction secondary to sarcoidosis is rare and often due to multiple etiologies including hypercalcemia, hypercalciuria and interstitial granulomatosis. Absence of interstitial granulomas does not preclude the diagnosis of sarcoid interstitial nephritis. Timely diagnosis and initiation of steroids can prevent further progression and can improve the renal function. We present 3 cases of sarcoidosis interstitial nephritis with and without granulomas in interstitium. All the cases mainly presented with generalized weakness and fatigue, who were found to have AKI and hypercalcemia. Our first case was thought to have AKI secondary to hypercalcemia, which resolved with iv hydration, and the patient was discharged. He was readmitted in 3 months for AKI and pancytopenia and was found to have sarcoidosis induced nephritis without interstitial granulomas on renal biopsy. His renal function improved significantly after treatment with steroids. The other two cases had an early diagnosis of sarcoid interstitial nephritis with granulomas demonstrated on renal biopsy. Renal function improved significantly with steroids. In this article, we have discussed our 3 cases along with review of literature between 2013 to 2018, with the primary aim of enforcing the need for early recognition and treatment of sarcoid induced nephritis with steroids which could significantly reduce both short and long-term morbidity and mortality associated with the disease.

Introduction

Sarcoidosis is an idiopathic multisystem granulomatous disease that has been postulated to be autoimmune etiology [1]. Incidence and prevalence of sarcoidosis is variable depending on geographic region and has been reported as 10 per 100,000 per year [2-4]. Highest incidence has been noted in the African American population [5]. Diagnosis is mostly dependent on a biopsy of an involved organ showing non-caseating granulomas as there is no reliable test to rule in or rule out this disease [6]. Lungs are most commonly involved but extra pulmonary manifestations have also been reported. Renal manifestation secondary to sarcoidosis are mostly due to hypercalcemia and hypercalciuria leading to nephrocalcinosis but clinically apparent renal failure is less common [1]. We present 3 cases of renal failure secondary to sarcoidosis and all them had features of interstitial nephritis on renal biopsy. Apart from the cases presented, we reviewed all cases of sarcoidosis induced interstitial nephritis reported from 2013 to 2018. There was a total of 13 case reports found that were reviewed. Sarcoidosis induced interstitial nephritis without granuloma formation has not been reported in the past 5 years which was observed in one of our cases. Once this condition is diagnosed, steroids with and without immunosuppressive agents play important role in the prognosis of renal sarcoidosis to prevent end stage renal disease (ESRD) [1,6].

Case 1

An 81-year-old Caucasian male was referred from the outpatient clinic for evaluation of hypercalcemia with a serum calcium level of 13.7 mg/dl that was performed to evaluate his generalized weakness and worsening confusion for 1-2 weeks. His past medical history was significant for bladder cancer status post-surgery. He was suspected to have malignancy related hypercalcemia. As a work up for malignancy, his CT scan abdomen and pelvis showed para aortic and left inguinal lymphadenopathy. His initial laboratory investigation revealed elevated serum creatinine of 2.07 mg/dl (Table 1). The patient’s acute kidney injury (AKI) was presumed to be secondary to hypercalcemia which improved with aggressive hydration. Fine needle aspiration of the left inguinal lymph node was inconclusive due to inadequate sampling. He was discharged after resolution of hypercalcemia and AKI. Outpatient bone marrow biopsy for evaluation of pancytopenia revealed non-caseating granulomas. Three months after initial hospitalization, patient was sent to emergency department again from primary care office for AKI and pancytopenia. On admission, he subjectively had generalized weakness although his physical examination was unremarkable, including vital signs. He was worked up for vasculitis and multiple myeloma which came back negative. Infectious causes of granulomatous disease including hepatitis panel, histoplasmosis, and tuberculosis were negative. Renal ultrasound showed bilateral increased echogenicity. Patient underwent renal biopsy due to suspicion for sarcoidosis induced interstitial nephritis. His calcium level improved to 9 mg/dL but creatinine remained persistently elevated (5.03 to 5.43) despite aggressive hydration. On patient request, he was discharged with plan for starting steroids as an outpatient. The renal biopsy showed tubular degenerative changes, interstitial edema, mild diffuse interstitial inflammation with multifocal mild to moderate lymphocytic tubulitis, mild tubular atrophy and interstitial fibrosis.

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A 30 years-old male without significant past medical history presented with fatigue, back pain, polydipsia and polyuria for 4–5 months. He also reported a 50 lbs. weight loss over 5 months. Physical examination was unremarkable except multiple palpable lymph nodes in axilla and inguinal region. Laboratory investigation revealed hypercalcemia, elevated BUN and serum creatinine levels (Table 1). He was admitted for acute renal failure. Computed Tomography (CT) chest, abdomen and pelvis showed extensive mediastinal, mesenteric, retroperitoneal lymphadenopathy. Inguinal lymph node biopsy was obtained which showed confluent epithelioid granulomas consistent with sarcoidosis. Auramine and AFB stains were negative for mycobacteria. GMS stain was negative for fungal pathogens. Angiotensin converting enzyme (ACE) level was elevated 111.7 U/L (9-67). Further workup ruled out hematologic malignancies and bone scan showed no skeletal mass. Renal biopsy was performed which showed severe acute and chronic interstitial nephritis with focal granulomatous features. Patient's renal function significantly improved after treatment with steroids.

### Discussion

Sarcoidosis is an idiopathic multisystem autoimmune inflammation that is most commonly seen in the African American population with the lungs most commonly involved [2,3]. Hypercalcemia and hypercalciuria leading to direct tubular damage and nephrothiasis play key role in its pathogenesis [5]. Renal dysfunction secondary to sarcoidosis is rare. Renal biopsy typically shows interstitial granulomas and reported to be found in 7 to 23 % of cases when autopsies of patients with sarcoidosis induced kidney injury are performed [7-9]. Most cases of sarcoid interstitial nephritis have been reported with renal biopsy showing non-caseating granulomas and not even one case was reported without granulomas in kidney except for one of our cases where renal biopsy showed interstitial inflammation but no granuloma (Table 3) [10-22].

In our 3 cases of sarcoid induced interstitial nephritis, there were 2 cases with granulomas in kidney and bone marrow and the other case of already diagnosed sarcoidosis who presented with renal dysfunction but there were no granulomas seen on the kidney biopsy.
All three had the common symptoms of weakness and fatigue and were found to have AKI and hypercalcemia. The first case primarily had granulomatous infiltration of the bone marrow but not the kidneys. He did have inguinal and para-aortic lymphadenopathy, but no other manifestations. His diagnosis was delayed. The second case had an early diagnosis and initiation of steroids compared to the previous case. Our third case was unusual with the predominant extra pulmonary manifestation of diffuse lymphadenopathy which raised a strong suspicion of lymphoma. Peripheral lymphadenopathy is common in younger patients and is seen in about 40% of patients with sarcoidosis. All our three cases had some form of lymphadenopathy. Most common form of lymphadenopathy seen is hilar and Para tracheal, present in almost 90% of patients [23,24]. However, our patient had mediastinal lymphadenopathy without hilar adenopathy which is very uncommon in sarcoidosis [25]. All our cases showed significant improvement in the renal function after treatment with steroids.

Apart from the cases presented, we reviewed all cases of sarcoidosis induced interstitial nephritis reported from 2013 to 2018. Thirteen cases were reviewed, 6 males and 7 females, with a mean age of 56 years. Most common symptom at presentation was weight loss followed by fatigue, malaise, fever, nausea, vomiting, lethargy and anorexia [10-22]. All patients presented with renal dysfunction with mean creatinine of 4.9 mg/dl. Proteinuria was reported in 7 patients and was not documented in 3 cases. Angiotensin converting enzyme level (ACE) was reported to be elevated in 6 patients and was not documented in one patient (Table 2). Hypercalcemia was reported in 6 patients at the time of presentation with no documentation of calcium level in one case (Table 2). Most common extra renal manifestation include lungs followed by lymph node, salivary glands, bone marrow, spleen and brain respectively [10-22]. Mediastinal lymphadenopathy was present in 46.15% of cases (Table 2). Renal biopsy revealed granulomatous interstitial nephritis in all 13 cases. Steroids were started as initial treatment in all thirteen cases and creatinine was followed. Creatinine levels normalized in 38.4 % cases 53.8% showed improvement in serum creatinine after initiating steroids [10-22].

There was one case reported of sarcoid induced interstitial nephritis with extra renal granuloma with eosinophilic tubulo-interstitial nephritis on renal biopsy and granulomas on liver biopsy [23]. There was also a case series of 94 cases of patients with sarcoid granulomatous interstitial nephritis from 1955 to 2005 which showed a mean age 46.9 [1]. This study explained various etiologies of sarcoidosis induced kidney damage including glomerular, tubular and interstitial damage secondary to hypercalcemia, hypercalciuria and granulomatous inflammation leading to clinically apparent renal failure [1]. Steroids played an important role in improving the prognosis in all cases reported in this case series [1].

Taro Horino et al. [10] reported the case with constitutional symptoms in a patient with history of uveitis for 2 years and renal failure on presentation as compared to our patient with no ophthalmologic presentation. Sarcoidosis has variable presentation...
and renal manifestation is rare. It can present with Lofgren syndrome that include arthralgia and erythema nodosum as seen in one of the cases found in which vasculitis and splenic nodules were shown as presentation of sarcoidosis along with salivary gland granulomas [11]. Parotid gland is the most common salivary gland involved that can present as painless bilateral cheek swelling or painful parotitis [16,18]. Hypercalcemia and elevated ACE levels are also helpful but not diagnostic as shown in less than 50% of the 13 cases studied. Bone marrow involvement is also not a common finding in sarcoidosis patients. Disturbance of renal functions with high suspicion of sarcoidosis should lead to renal biopsy as was performed in all cases studied. The findings of interstitial nephritis with granuloma formation was found in all except our case which showed no granulomas but presence of lymphocytic inflammation, tubulitis and tubular atrophy. Other renal biopsy findings may include glomeruli with focal ischemic tuft retraction and interstitial fibrosis [11-14]. Anti-glomerular basement membrane (GBM) antibodies should be tested as co-occurrence of Anti GBM antibodies in renal sarcoidosis was reported by in one of the cases reviewed in which no other light microscopic findings were found consistent with anti GBM antibodies [20]. Steroids are the main stay of treatment once the diagnosis is made. All our patients responded to steroids and renal function improved. Steroid sparing agents such as azathioprine can be used for those cases with gradual improvement to avoid the devastating side effects from long term steroid use [11,16].

Since 2006 comprehensive review by Berliner et al. [1], many more cases have been reported. This is updated review in which 13 cases with enough reportable data were found and studied. All cases were presented with granuloma formation on kidney biopsy except for the one of our cases which did not have granulomas on renal biopsy. This is a unique finding from other cases with granulomas reported between 2013 and 2018.

Conclusion

Sarcoidosis induced interstitial nephritis is always a concern for internist and nephrologist but is often diagnosed late in the clinical course. Presence of interstitial granulomas is the most common finding of Sarcoid interstitial nephritis but it can be diagnosed without presence of granulomas in the right clinical setting as in our case. The absence of granulomas should not delay the treatment as it can lead to worse clinical prognosis with ESRD. This updated review of literature is to facilitate internists for prompt initiation of corticosteroids, early renal biopsy in a clinical situation concerning for sarcoidosis with renal failure and not exclude sarcoidosis induced interstitial nephritis even without the presence of granulomas.

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