Sarcoidosis induced interstitial nephritis. A case series with literature review

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Abstract

Sarcoidosis is an idiopathic 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].

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].
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Table 1. Summary of Laboratory results

| Laboratory data | Case 1 | Case 2 | Case 3 | Reference Range |
|-----------------|-------|-------|-------|-----------------|
| BUN             | 28    | 57    | 55    | 5.25 mg/dL      |
| Creatinine      | 2.07  | 4.0   | 5.23  | 0.62-1.24 mg/dL |
| GFR             | 31    | 6     | 11    | >60             |
| Calcium         | 14.0  | 14.3  | 14.0  | 8.5-10.5 mg/dL  |
| Albumin         | 3.6   | 3.6   | 2.4   | 3.5-5.0 g/dL    |
| Hemoglobin      | 13.1  | 11.7  | 9.9   | 12-17.5 g/dL    |
| WBC             | 5.4   | 5.8   | 3.2   | 4.5-11.6 K/uL   |
| Platelet count  | 214   | 265   | 115   | 140-450 K/uL    |
| SPEP            | -*    | -*    | -*    | 0.0-4.0 ng/mL    |
| PSA             | 9.76  | 0.3   | 0     | 38-126 ng/mL    |
| ALP             | 249   | 47    | 176   | 5-100 ng/mL     |
| 25- OH vitamin D| 65    | 6     | 27    | 8.5-10.5 mg/dL  |
| 1-25 dihydroxy vitamin D | 152 | 5.8 | 18.0 | 19.9-79.3 pmol/L |
| ACE level       | 92    | 166   | 111.5 | 9-67 U/L        |
| PTH             | 8.8   | 6     | 16.8  | 12-88 pg/mL     |
| PTHrp           | 4.3   | <0.3  | -0.3  | 0.2-2.3 pmol/L  |
| ANA             | -0.62 | -     | -     | <0.90           |
| ANCA            | -     | -     | -     | -               |
| Urine total protein | 1330 | 5-100 mg/24 hours | 5-100 mg/24 hours | 0.10-10 mg/mL |
| CEA level       | 2.1   | -     | -     | 4-7.0 mg/dL     |
| CEA level       | -     | -     | -     | 4-7.0 mg/dL     |
| AFP             | <2.5  | <2.5  | <2.5  | <9.0 ng/mL      |

Empty cells mean no data available. BUN: Blood urea nitrogen. GFR: Glomerular filtration rate. WBC: White blood cells. SPEP: Serum protein electrophoresis. PSA: Prostate specific antigen. ALP: Alkaline phosphatase. 25 OH Vitamin D: 25 hydroxy vitamin D. ACE: Angiotensin converting enzyme. PTH: Parathyroid hormone. PTHrp: PTH related peptide. ANA: Anti-nuclear Antibody. ANCA: Anti-neutrophil cytoplasmic antibody. CEA: Carcino-embryonic antigen. AFP: Alpha feto protein. * Negative result

and microscopic tubulopapillary lesion, suggestive of sarcoidosis induced interstitial nephritis. After treatment with steroids creatinine significantly improved (3.03 mg/dL) on repeat blood work one month after discharge.

Case 2

A 62 years-old male with no significant past medical history, initially presented with sleepiness, weakness, polyuria, low-grade fever for 2-3 weeks and 100 lbs. weight loss over a 2-year period. Physical examination was unremarkable. Laboratory investigations revealed elevated blood urea nitrogen, serum creatinine level and hypercalcemia (Table 1). He was admitted due to AKI in the setting of hypercalcemia, elevated blood urea nitrogen 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 epitheloid 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 nephrolithiasis 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-casing 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.

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| WBC             | 5.4   | 5.8   | 3.2   | 4.5-11.6 K/uL   |
| Platelet count  | 214   | 103   | 265   | 140-450 K/uL    |
| SPEP            | -*    | -*    | -*    | 0.0-4.0 ng/mL    |
| PSA             | 9.76  | 0.3   | 0     | 38-126 ng/mL    |
| ALP             | 249   | 47    | 176   | 5-100 ng/mL     |
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| Urine total protein | 1330 | 5-100 mg/24 hours | 5-100 mg/24 hours | 0.10-10 mg/mL |
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| CEA level       | -     | -     | -     | 4-7.0 mg/dL     |
| AFP             | <2.5  | <2.5  | <2.5  | <9.0 ng/mL      |
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.

### Table 2. Summary of 13 Reported Cases of Sarcoid induced interstitial nephritis

| Source                  | Age (y)/Sex | Creatinine (mg/dl) | Proteinuria* | Elevated Serum Calcium (>11 mg/dl) | Serum ACE | Mediastinal adenopathy |
|-------------------------|-------------|--------------------|--------------|-----------------------------------|-----------|------------------------|
| Taro et al. [10]        | 62F         | 4.56               | +(1.4g/g)    | +                                 | -         | +                      |
| Amel et al. [11]        | 35F         | 6.06               | (<0.5g/day)  | -                                 | -         | +                      |
| Hirouki et al. [12]     | 60F         | 4.2                | -            | +                                 | -         | -                      |
| Varun et al. [13]       | 66M         | 5.4                | -(1+)        | -                                 | -         | -                      |
| Joana et al. [14]       | 26F         | 2.0                | +(0.3g/24hrs) | +                                 | +         | +                      |
| Hirouki et al. [15]     | 70M         | 2.39               | -(1+)        | -                                 | -         | -                      |
| Nagaraja et al. [16]    | 56F         | 3.0                | -(0.24g/24h) | +                                 | +         | +                      |
| Amel et al. [17]        | 37F         | 5.4                | +            | +                                 | +         | +                      |
| Tamires et al. [18]     | 65M         | 8.65               | +(0.5g/l)    | +                                 | +         | +                      |
| Saika et al. [19]       | 55M         | 7.6                | +            | +                                 | +         | +                      |
| Yoshinori et al. [20]   | 77F         | 3.19               | -(0.4g/24h)  | -                                 | +         | +                      |
| Sharica et al. [21]     | 44M         | 3.42               | +(1070mg/g)  | +                                 | -         | +                      |
| Shinichiro et al. [22]  | 79M         | 7.97               | +            | +                                 | -         | -                      |

Empty cell means no data available. ACE: Angiotensin converting enzyme, * Data in uniform units for proteinuria not available.

### Table 3. Summary of Renal Biopsy and Extra-renal manifestation in 13 Reported Cases

| Source                  | Granulomas on biopsy | Extrarenal manifestation |
|-------------------------|----------------------|-------------------------|
| Taro et al. [10]        | +                    | +                       |
| Amel et al. [11]        | +                    | -                       |
| Hirouki et al. [12]     | +                    | +                       |
| Varun et al. [13]       | +                    | +                       |
| Joana et al. [14]       | +                    | +                       |
| Hirouki et al. [15]     | +                    | +                       |
| Nagaraja et al. [16]    | +                    | +                       |
| Amel et al. [17]        | +                    | +                       |
| Tamires et al. [18]     | +                    | +                       |
| Saika et al. [19]       | +                    | -                       |
| Yoshinori et al. [20]   | +                    | +                       |
| Sharica et al. [21]     | +                    | +                       |
| Shinichiro et al. [22]  | +                    | +                       |

Empty cells means no data available.
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 rejections 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 mainstay 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 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 associated with sarcoidosis. CEN Case Rep 7: 34-38. [Crossref]

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