Renal Sarcoidosis and Multiple Myeloma
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Abstract
An association between sarcoidosis and multiple myeloma (MM) has been reported in several case reports. In these cases, sarcoidosis is chronically active, systemic, diagnosed at a later age than controlled groups, and often precedes the diagnosis of multiple myeloma by several years. We present the first case of a 43-year-old asymptomatic man with abnormal renal function and monoclonal gammopathy who was simultaneously diagnosed with renal sarcoidosis and MM. He was successfully treated with Thalidomide and steroids and remains in remission after two years of follow up. Pathophysiology of sarcoidosis and MM with special focus on potential link between the two diseases is discussed.

INTRODUCTION
Sarcoidosis is a chronic inflammatory disease with clinically significant renal involvement mostly due to hypercalcemia (10%) and hypercalciuria (50%).\(^1\) Up to 20% of sarcoidosis patients show granulomatous interstitial nephritis on biopsy and autopsy reports.\(^2\) An association between sarcoidosis and malignancy has been suggested.\(^3\) Hodgkin’s disease and non-Hodgkin lymphoma encompass the majority of cases that highlight this association.

Less commonly, monoclonal gammopathies have been reported in association with sarcoidosis. There are eleven case reports of multiple myeloma (MM) in association with sarcoidosis in the literature.\(^4\) None of these cases report renal involvement. We describe a patient with simultaneous presentation of renal sarcoidosis and MM. We discuss the atypical presentation, pathophysiology and highlight the importance of performing a renal biopsy.

CASE REPORT
A 43-year-old African-American male with no prior medical history was referred to outpatient nephrology clinic for evaluation of abnormal renal function found on routine health exam. Serum creatinine level was 2.4 mg/dL. Review of systems were unremarkable. His blood pressure was 138/104 mmHg. Physical examination findings were unremarkable. A complete blood count showed a white blood cell count of 4.5 x 10^9 L, hemoglobin 13.3 g/dL and platelet count of 135 x 10^9 L. Serum calcium was 9.5 mg/dL with an albumin of 3.9 g/dL and a total protein level of 9.7 g/dL. Urinalysis showed trace blood and 1+ protein with no cellular casts. He had 480 mg of proteinuria on a 24 hour urine collection. Urine calcium to creatinine ratio was within normal range (121 mg/L). Both serum and urine protein electrophoresis with immunofixation revealed monoclonal Immunoglobulin (Ig) G lambda. Quantitative serum Igs showed 43 g/L (normal range, 6-16 g/L) of IgG and normal levels of IgA and IgM. Lambda free light chains were elevated at 96.3 mg/L (normal range, 5.17-26.3 mg/L) with normal kappa free light chains of 17.8 mg/L (normal range, 3.3-19.4 mg/L). Skeletal survey radiography was negative for osteolytic bone lesions.

Bone marrow biopsy and aspiration was consistent with MM without any evidence of granulomas. Percutaneous renal biopsy showed areas of non-caseating granulomatous interstitial nephritis involving approximately 50% of the cortex and medulla (Figure 1). The uninvolved areas of cortex contained 17 glomeruli and were unremarkable by light and immunofluorescent microscopy. The tubules were free of casts (Figure 2). Stains for acid fast (Fite’s) and fungal (GMS) were negative. The congo red stain in both the bone marrow and renal tissues were negative. Infectious workup including urine and sputum cultures for acid fast bacilli was negative. Serum Angiotensin Converting Enzyme (ACE) level was elevated at 81 U/L with a normal 1,25-dihydroxy Vitamin D level of 23 pg/ml. Computed Tomography scan of the chest, abdomen and pelvis revealed
hilar and para-aortic abdominal lymphadenopathy consistent with the diagnosis of sarcoidosis.

The patient was started on prednisone at 1mg/kg for treatment of renal sarcoidosis. He was subsequently switched to Thalidomide and Dexamethasone for treatment of multiple myeloma and remained on this therapy for 5 months. After two years of follow up, his serum creatinine was 2.15 mg/dL. Quantitative serum IgG had decreased to 21 g/L. He remains asymptomatic without any signs of anemia or hypercalcemia.

**Figure 1**

Fig 1. Granulomatous interstitial nephritis. Ischemic glomerulus surrounded by isolated atrophic tubules and granulomatous inflammation with sheets of epithelioid histiocytes. On the right side of the picture is a well-formed granuloma. PAS x132.

**Figure 2**

Fig 2. Granulomatous interstitial nephritis. Renal tubule surrounded by granulomatous inflammation with sheets of epithelioid histiocytes. The tubule shows tubulitis with lymphocytes invading the tubular epithelium. PAS x132.

**DISCUSSION**

MM is a lymphoid neoplasm resulting from genetic changes in late B-cell differentiation. The incidence of MM is estimated at 4.2 per 100,000 population and patients 40-49 years of age comprise 8% of these cases. The etiology of MM is unknown, however, in addition to environmental exposures, chronic inflammatory diseases leading to prolonged stimulation of the reticuloendothelial system in animal models have been implicated.

Sarcoidosis, a multiorgan granulomatous inflammatory disease, has been linked to increased activity of macrophages and CD4+ Th cells. In addition to infectious causes such as mycobacterial and propionibacterial organisms, mutations of butyrophilin-like 2 (BTNL2), an MHC class II gene-linked butyrophilin-like molecule have been linked to sarcoidosis. The annual incidence of sarcoidosis is 35 per 100,000 in the African-American population. Based on these figures, the coincidental occurrence of MM and sarcoidosis in the same patient is rare and may suggest a causal relationship.

Two competing theories have attempted to explain the observed association between MM and sarcoidosis. The original hypothesis suggests that active chronic inflammation from sarcoidosis is responsible for chronic activation of CD4+ Th cells and decreased CD8+ T suppressor cells, which result in continuous stimulation of B-cells and subsequent malignant transformation. The counter hypothesis using linkage-analysis proposes a
systemic sarcoid-like reaction to malignancy. In nine of the twelve reported cases, sarcoidosis preceded the diagnosis of MM, which supports the original hypothesis of sarcoidosis as a potential cause for malignancy. The B7 superfamily of receptors that are upregulated in antigen-presenting cells, such as macrophages, have been shown to play a crucial role in sarcoidosis.\(^1\) The interaction between B7 receptors and CD28 on naïve T-cells is a co-stimulatory signal for cell activation and tolerance.\(^13\) However, CD28 is present on some malignant plasma cells and its expression in MM patients is associated with disease progression and treatment failure, a potential common link between the two diseases.\(^14\)

The common themes in the eleven previously reported cases of sarcoidosis and MM are chronic active sarcoidosis, diagnosis of MM an average of 6 years (range 2-27 years) after the diagnosis of sarcoidosis, and older age of patients (56 years) at the time sarcoidosis was diagnosed as compared to unselected sarcoidosis patients.\(^4\) The current case has an atypical presentation that challenges these previously observed features. Our patient presented at a younger age of 43, not atypical for sarcoidosis but rather rare for MM. In addition, to our knowledge, this is the only case of MM and renal sarcoidosis. There was no evidence of paraproteinemia-associated renal lesion or granulomatous involvement of the bone marrow. The diagnosis of sarcoidosis and MM were made simultaneously, although the patient likely had undiagnosed renal sarcoid for an unknown period of time given the degree of chronic interstitial fibrosis.

This case highlights the importance of performing a renal biopsy in the setting of paraproteinemia. Paueksakon et al. studied the renal biopsies of 87 patients with monoclonal gammopathy and found 63% of this group had renal disease unrelated to the paraproteinemia.\(^15\) With the bone marrow findings of MM, if assumed that the renal insufficiency was paraprotein-related, the diagnosis of sarcoidosis would have been missed.

Recently, the French Sarcoidosis Group reported 47 cases of biopsy-proven renal sarcoidosis. Renal sarcoidosis has a high prevalence of hypercalcemia, which was not a feature of our patient. More importantly, the predictors of long-term renal outcome in steroid-treated renal sarcoidosis patients are directly related to response at 1 month and inversely related to the degree of interstitial fibrosis.\(^16\) In our patient, despite steroid therapy, serum creatinine continued to rise for the first 3 months of therapy before it stabilized and subsequently returned to pre-treatment values. This incomplete renal response seen at one month and two-year follow up is explained by the significant interstitial fibrosis (>50%) on renal biopsy.

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**References**

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