Sarcoidosis-Associated Immune Thrombocytopenic Purpura and Focal Segmental Glomerulosclerosis

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Abstract
Sarcoidosis is well known for heterogeneity of its presentation and multisystem organ involvement. It commonly involves respiratory tract, skin, eyes, and lymph nodes, as well as hematologic and renal systems. While anemia and lymphopenia are the most common hematologic abnormalities seen in sarcoidosis, immune thrombocytopenic purpura (ITP) is considered rare. Renal abnormalities, although infrequent, are usually more likely to involve tubules rather than glomeruli. In this report, we present a case of sarcoidosis-associated ITP and focal segmental glomerulosclerosis (FSGS), refractory to first-line therapy, but successfully treated with Rituximab and thrombopoietin-receptor agonist.

Keywords
sarcoidosis, immune thrombocytopenic purpura (ITP), focal segmental glomerulosclerosis (FSGS)

Case Description
A 32-year-old male with known multisystem sarcoidosis presented to the emergency room with complaining of hematemesis, bruising, epistaxis, and generalized weakness. At the time of his initial diagnosis of sarcoidosis 5 years ago, patient underwent bone biopsy which showed noncaseating granulomas with associated fibrosis. Patient was lost to outpatient follow-up and was not on any home medications. On the physical exam, patient had petechiae, ecchymosis, and plaques with papules, located on his extremities, suggestive of active sarcoid skin lesions. On complete blood count, patient had thrombocytopenia 3000/uL, and basic metabolic panel was significant for acute kidney injury (creatinine = 3.25 mg/dL, baseline creatinine = 2.0 mg/dL) with subnephrotic range proteinuria (total urine protein-to-creatinine ratio 1098 mg/g). Patient did not have laboratory signs of hemolysis, and his direct Coombs test was negative. He underwent robust infectious workup, which included HIV, COVID-19, and hepatitis panel, and results were negative. Imaging studies were remarkable for mild splenomegaly and an increased number of subcentimeter hilar and mediastinal lymph nodes, seen on the computed tomography (CT) of chest, abdomen, and pelvis. Patient was started on Dexamethasone 30 mg daily for 4 days and 2 g/kg of intravenous immunoglobulin for presumed diagnosis of immune thrombocytopenic purpura (ITP) with subsequent improvement in platelet count to 42 000/uL. Acute kidney injury and proteinuria workup showed a positive antinuclear antibody (ANA) (1:160), low complement levels (C3–48 mg/dL, C4–14 mg/dL), and elevated angiotensin-converting enzyme (ACE) level (>80 U/L). Testing for anti-neutrophil cytoplasmic antibody (ANCA) and anti-phospholipid panel was negative. Due to severe thrombocytopenia, patient was not a candidate for renal biopsy at that time. He was discharged home, but was re-admitted 15 days later for severe thrombocytopenia of 1000/uL, epistaxis, and bruising. Similarly, he received high-dose steroids (Dexamethasone 40 mg) and intravenous immunoglobulin (1 g/kg), but did achieve an appropriate clinical response. He was started on Rituximab 375 mg/m2 once a week along with Eltrombopag (thrombopoietin receptor agonist) for his refractory ITP. As a result, platelet count improved to 80 000/uL. Renal biopsy was performed and 17 glomeruli were available for assessment. It
showed focal and segmental glomerulosclerosis with classic or not otherwise specified (NOS) histologic variant along with mild interstitial fibrosis and tubular atrophy. One out of 17 glomeruli showed global sclerosis. Immunofluorescence microscopy did not reveal IgG, IgA, IgM, IgG4, complements, Kappa and Lambda light chains, and fibrinogen depositions. Electron microscopy showed moderate effacement of podocytes foot processes and focal thickening of glomerular basement membranes. The findings above were described as likely secondary FSGS.

Overall clinical picture, given his active skin lesions, extensive lymphadenopathy, thrombocytopenia, and renal involvement with elevated ACE levels, was consistent with active multisystem sarcoidosis. In this case, ITP signs and symptoms developed approximately 60 months after initial diagnosis of Sarcoidosis.

On discharge, patient’s platelet count increased to 177 000/uL and remained stable thereafter and renal function was also stabilized at Cr 1.67 mg/dL. (Table 1) After discharge, the patient received slow steroid taper along with Eltrombopag (thrombopoietin receptor agonist) 25 mg every other day with no recurrence of ITP. His renal function remained stable.

Discussion

Sarcoidosis is a chronic granulomatous disorder with multisystem involvement characterized by noncaseating epithelioid granulomas. It typically presents in third or fourth decade with slight predilection for female gender. It is thought that sarcoidosis most commonly affects patient of African Americans and North European origin. It usually involves lungs, skin, lymph nodes, and eyes, but involvement of other organs has been reported.

Jersild3 reported the very first case of sarcoidosis-associated ITP in 1938. There are 3 main mechanisms that are believed to be responsible for the ITP associated with sarcoidosis: hypersplenism, bone marrow infiltration, and antibody mediated platelet destruction. Our patient had evidence of both hypersplenism and bone marrow infiltration, which could explain his thrombocytopenia. In a case-series of 20 patients described by Mahévas et al, the time course between sarcoidosis and ITP was variable.8 ITP presentation has been reported preceding, concomitantly, and after the diagnosis of sarcoidosis. In this case series, 55% of patients had a diagnosis of sarcoidosis preceding ITP onset, similar to our case. The median time from sarcoidosis to ITP was 48 months (range 6-216 months) in the study, compared with 60 months in our patient. Of the 11 patients who had sarcoidosis preceding ITP, 2 were thought to be in remission when they presented with ITP, similar to our patient. The first line of therapy frequently used for ITP is 1 mg/kg of prednisone per day with or without an intravenous immunoglobulin.9 The second-line therapy might include an addition of an alternative immunosuppressive agent like Rituximab.5,10 In more severe cases of resistant ITP, splenectomy is described as the last resort treatment and has shown to be effective majority of patients.5 Our patient initially responded to high-dose steroids and intravenous immunoglobulin, but relapsed within 2 weeks. Fortunately, he responded to combination of Rituximab and Eltrombopag resulting in normalization of his platelet count.

The underlying mechanism for development of FSGS in sarcoidosis is not well understood, but T-cell dysfunction and immune complexes deposition are thought to be the 2 primary pathogenic pathways.11 Our patient’s biopsy results were not consistent with immune complex deposition and showed only mild interstitial inflammatory changes. Partially, this could be explained by sampling problem: segmental lesions are likely to be present in a scarce proportion of glomeruli.12 Another hypothesis is that the disruption in glomerular membrane permeability could be caused by increased cytokine production by sarcoid granulomas.13 Primary cytokines described in this process are tumor necrosis factor (TNF)-alpha, interleukin (IL)-1, and IL-2.6,13,14

The effectiveness of steroid therapy for FSGS is unclear. In 2 cases of FSGS described in the literature, the kidney function worsened despite aggressive steroid therapies, and the patients had to undergo renal transplantation. However, some patients exhibit positive response to steroid therapy for FSGS.11,15 According to Kaaroud et al,16 tubulointerstitial
nephritis is more responsive to corticosteroid therapy in comparison with glomerulonephritis.

Our patient does not have significant proteinuria and his renal function has remained stable so it is plausible that Rituximab and high-dose steroids might have been renoprotective to some degree. After discharge patient was on slow steroid taper and on Eltrombopag 25 mg 2 times a week with no recurrence of ITP and stable renal function. Based on patient’s clinical course, a further decision on whether the patient needs another cycle of Rituximab will be made.

Conclusion

ITP and FSGS are rare manifestations of sarcoidosis which can potentially pose a both diagnostic and therapeutic challenge. Our case describes the successful treatment of sarcoidosis with Rituximab and Eltrombopag.

Authors’ Note

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Ethics Approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent

Verbal informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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