CLINICAL VIGNETTE

Autoimmune Myelofibrosis and Lupus

Tamara Dahhan, DO and Melissa J. Cohen, MD

Introduction

Autoimmune myelofibrosis (AIMF) is a rare disorder characterized by cytopenia and bone marrow fibrosis, that can occur by itself, or in association with systemic autoimmune disease.[1,2] It is often an under recognized clinical entity, and is commonly mistaken for Primary Myelofibrosis (PMF) or cytopenia related to other autoimmune phenomena.[1] Distinguishing PMF from AIMF is very important, as these diseases vary greatly in their clinic course, treatment, and prognosis.[3]

In contrast to autoimmune myelofibrosis, primary myelofibrosis is a myeloproliferative disorder, caused by a clonal proliferation of one or more subtypes of myeloid cells causing fibrosis and neovascularization of the bone marrow.[1] Clinical features include progressive anemia, constitutional symptoms, hepatosplenomegaly, extramedullary hematopoiesis, and potential leukemic progression. The peripheral blood smear often demonstrates multiple RBC abnormalities including teardrop cell, nucleated red blood cells, as well as leukoerythroblastosis and large platelets. The majority of patients with primary myelofibrosis will have a genetic mutation in JAK, CALR, or MPL, however 8-10% of cases may be triple negative for mutation.[4]

It is important to note that bone marrow fibrosis can occur in the setting of neoplastic diseases such as myeloproliferative diseases, but can also occur in other neoplastic diseases such as leukemia, lymphoma and metastatic solid tumors.[1] Non-neoplastic causes of bone marrow fibrosis include infection, drug reactions, nutritional deficiencies and, as in our case presentation, autoimmune disease.[1,5]

We present a patient with autoimmune myelofibrosis secondary to Systemic Lupus Erythematosus (SLE) that had transformed from Mixed Connective Tissue Disease (MCTD). Autoimmune myelofibrosis has been reported in SLE, although it is known to be a rare disease complication. Distinguishing autoimmune myelofibrosis from primary myelofibrosis can be challenging, but is critical for deciding on effective treatment.

Case Presentation

A 40-year-old African American female, with a history of Mixed Connective Tissue Disease (MCTD), presented to the rheumatology clinic after recent hospital admission. The patient had been given the diagnosis of MCTD five years prior, with disease features including positive antinuclear antibody (ANA), positive anti-ribonucleoprotein (anti-RNP), photosensitive rash and inflammatory arthritis. She had been treated with hydrochloroquine for one year, but was later lost to follow up and discontinued the medication. In the 6 months leading to the hospitalization the patient noted rapidly progressing diffuse patchy alopecia, intermittent subjective fevers, unintentional weight loss and fatigue. She was seen by her primary care doctor who noted diffuse lymphadenopathy in the cervical, supraclavicular, axillary and inguinal regions, and she was referred to hematology-oncology for further evaluation.

The patients CBC showed white blood cell count (WBC) 5.9, hemoglobin (Hgb) 9.4 with normal MCV, and platelets of 433. CBC three years prior showed normal hemoglobin and platelet count. Additional labs were notable for normal B12, folate, Vitamin D, TSH, and LDH. Direct Coombs test was negative. HIV, RPR, Quantiferon Gold and an acute hepatitis panel were negative. Abnormal labs included elevated ESR 78 mm/hr, CRP 1.7mg/dL, haptoglobin 404 mg/dL, D-Dimer 3,119 ng/mL, ferritin 466 ng/mL. Iron was low at 36 mcg/dL and TIBC was also low, 195 mcg/dL. PT/PTT were normal and Reticulocyte count was in the normal range. There was a polyclonal gammopathy with elevated IgA and IgG. Serum protein electrophoresis was without monoclonal proteins and kappa/lambda ratio was normal. Colonoscopy to evaluate her iron deficiency anemia demonstrated large non-bleeding internal and external hemorrhoids. The patient was also referred for excisional lymph node biopsy as well as PET/CT, although these studies were not completed as the patient was lost to follow up.

Four months later the patient presented to the hospital for recurrent fevers up to 104.2 F and severe constipation. She had elevated lactate and was admitted, and started on IV fluids and empiric antibiotics. CBC showed a WBC 5.9, Hgb 8.2 MCV 77, and platelets 321. Blood and urine cultures were negative. CT imaging of the chest, abdomen and pelvis demonstrated diffuse lymphadenopathy, but no masses or splenomegaly. She underwent an excision inguinal lymph node biopsy, with pathology showing no evidence of lymphoproliferative malignancy or metastatic disease, and a negative flow cytometry. Serologies done during her admission demonstrated a positive ANA>1:1280 and RNP similar to previous, but now with new positive Smith antibody to 33 and double stranded DNA antibodies IFA 1:10 with normal C3 and C4. Ribosomal P, SSA/B, scl-70, centromere and ANCA antibodies were all

negative. Her creatinine was normal with urinalysis showing 1+ protein, but no microscopic hematuria. Her fevers later resolved and empiric antibiotics were stopped. No corticosteroids were given. She was discharged to follow up with Rheumatology.

At rheumatology follow up, the patient remained free of recurrent fevers since discharge. She continued to have alopecia, and mild joint pains in her hands and wrists. She denied any oral ulcers, rashes, Raynauds, chest pain, shortness of breath, or hematuria. On examination the patient was afebrile with normal vital signs. She had ongoing diffuse patchy alopecia with underlying patchy erythema of the scalp and inner ears. Large palpable lymph nodes were noted in the cervical, supraclavicular, axillary and inguinal regions. Cardiovascular and pulmonary exams were normal. There was mild swelling and tenderness in scattered proximal interphalangeal joints and bilateral wrists, with no other swollen or tender joints. There was no malar rash, oral or nasal ulcers. Laboratory data showed slightly improved Hgb of 9.4mg/dL. LDH was normal. Beta-2-microglobulin was elevated to 6. SPEP and UPEP were repeated and positive for a monoclonal band was noted in the gamma region. SPIF showed monoclonal IgG kappa protein, with elevated K/L ratio to 3.7. Hydroxychloroquine 400mg daily was started for her mild arthritis and patient was referred to Oncology too for further evaluation of ongoing anemia, lymphadenopathy, as well as new monoclonal IgG kappa protein with elevated K/L ratio.

Bone marrow biopsy demonstrated hypercellular marrow with myeloid hyperplasia, megakaryocytes with dysplastic changes suggestive of myeloproliferative neoplasm. Grade 3 bone marrow fibrosis was also noted, with reactive plasmacytosis with no light chain restriction. Iron stores were increased. No flow cytometry was done as bone marrow aspiration was dry. Peripheral blood testing was negative for JAK 2, MPL, CALR mutation. Peripheral flow cytometry showed no excess blasts, pan T cell aberrancies or monotypic B cell population. Given those results, there was no evidence of multiple myeloma, metastatic disease or primary myeloproliferative disorder, and the possibility of autoimmune myelofibrosis secondary to SLE was considered. CT/PET scan showed extensive, intensely hypermetabolic bulky lymphadenopathy throughout the neck, chest, abdomen, pelvis and groin. Repeat excisional lymph node biopsy showed reactive lymph nodes with follicular and interfollicular hyperplasia.

A renal biopsy was performed to evaluate and elevated urine protein to creatinine ratio of 1 gram with normal Creatinine, and demonstrated Class 1 SLE nephritis with immune complex deposition in the mesangial region with “full house” staining profile on immunofluorescence. No interstitial fibrosis was noted with normal glomeruli and renal cortex. The patient was diagnosed with autoimmune myelofibrosis, reactive lymphadenopathy and renal disease due to systemic lupus erythematosus.

The patient was started on high dose corticosteroids with taper, resulting in rapid improvement in her hemoglobin to the normal range. Mycophenolate mofetil was added as a disease modifying anti-rheumatic drug, to treat organ threatening SLE affecting the bone marrow, and Hydroxychloroquine was continued. Since initiation of treatment the patient's Hemoglobin has remained in the normal range after Prednisone taper and her alopecia is slowly resolving. Her fevers and lymphadenopathy have resolved.

Discussion

This case demonstrates a presentation of autoimmune myelofibrosis secondary to SLE. While this disease manifestation has been previously reported in Lupus, it is considered relatively rare, with fewer than 50 reported cases of SLE related myelofibrosis.[6] These patients may be misdiagnosed with primary myelofibrosis or as having a lupus associated cytopenias related to peripheral destruction, which is commonly seen in SLE.[7]

Clinical features of autoimmune myelofibrosis include cytopenia of one or more cell lines, as well as bone marrow biopsy demonstrating bone marrow fibrosis with increased reticulin fibers and fibroblasts.[7] Unfortunately, these pathological findings are indistinguishable from primary myelofibrosis. However, there are morphological criteria that favor AIMF over PMF that have been proposed, see Table 1.[8] Additionally genetic mutations testing for myeloproliferative disorders are negative, including commonly tested mutations such as JAK 2, MPL, CALR mutation. While this does not completely rule out primary myelofibrosis, it does help in the majority of cases. Evaluation for other neoplastic processes, such as lymphoma and leukemia, should be negative.

When the bone marrow fibrosis is demonstrated to be a non-clonal process, other causes such as autoimmune disease, nutritional deficiencies and medication related cytopenias should be considered. It is important to evaluate for clinical features of connective tissue disease. Lupus, as well as systemic sclerosis and sjogrens have all been described to cause AIMF.[5]

The prognosis of autoimmune myelofibrosis with treatment is favorable.[6] Initial treatment starts with corticosteroids and cytopenias are generally responsive as demonstrated in our case. On review of previous case reports multiple different disease-modifying antirheumatic drugs (DMARDs) have been used for long term disease control, including azathioprine, mycophenolate mofetil, cyclosporine as well as rituximab.[7,9] Tapering off corticosteroids has resulted in disease relapse in some cases.[5]

The specific features of our case include an isolated progressive anemia, with evidence of active connective tissue disease including alopecia, inflammatory arthritis, as well as early SLE Class 1 Nephritis. Additional autoimmune phenomena include new dsDNA and Smith positivity, demonstrating transformation from MCTD to SLE. The patient’s rapid improvement of her anemia with administration of high dose corticosteroids,

followed by stability of her blood counts on mycophenolate mofetil, demonstrate these treatments are effective.

Conclusion

In conclusion, the diagnosis of autoimmune myelofibrosis is centered on an evaluation for underlying connective tissue disease, as well as performing mutation analysis to evaluate for primary myelofibrosis. It is equally as important to evaluate for other malignancies including lymphoma and solid tumors, which can also provoke myelofibrosis. Treatment with cortico-steroids followed by the addition of a DMARD is the standard of care. The prognosis of autoimmune myelofibrosis with treatment is favorable.

Table 1 (adapted from Vergara-Lluri et al[8])

Morphologic Criteria for AIMF	Morphologic Criteria for PMF
Rarity or absence of leukoerythroblastic reaction in the peripheral blood, including abscess of teardrop cells, nucleated RBC and blasts	Prominent leucoerythroblastic reaction including presence of teardrop cells, nucleated RBC and blasts
Absence of peripheral eosinophilia or basophilia	Peripheral eosinophilia and basosphilia may be present
Mild degree of bone marrow fibrosis	Moderate to severe fibrosis
Absence of osteosclerosis and bone changes	Osteosclerosis may be present
Presence of hypercellular marrow characterized by erythroid and megakaryocytic hyperplasia	Presence of hypercellular marrow characterize by granulocytic hyperplasia
Presence of lymphoid aggregates	Rare presence of lymphoid aggregates

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