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Pulmonary Tuberculosis Reactivation and CNS Involvement Following Treatment of Myelofibrosis with Ruxolitinib: Case Report and Review of the Literature of Incidence in Myeloproliferative Neoplasms

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Abstract

A 69-year-old man with primary myelofibrosis was being treated with ruxolitinib for worsening constitutional symptoms. While ruxolitinib provided rapid symptom relief, he developed hemoptysis and changes to chest imaging. Comprehensive evaluation was diagnostic of mycobacterium tuberculosis with eventual progression to the central nervous system. Here we report the successful treatment of tuberculosis reactivation and describe the incidence of mycobacterium tuberculosis infection during treatment with ruxolitinib. Clinicians should consider risk of opportunistic infections when treating patients with myeloproliferative neoplasms with immunosuppressant medications such as ruxolitinib.

Keywords: *myelofibrosis, myeloproliferative neoplasm, mycobacterium tuberculosis, ruxolitinib*

Case Presentation

A 69-year-old African American man with Hepatitis C was treated with ledipasvir/sofosbuvir for 12 weeks in July 2015. He was referred to Hematology clinic for mild thrombocytosis (376 K/uL) and normocytic anemia (13.5 g/dL) in May 2016. Evaluation in Hematology Clinic eventually led to a bone marrow biopsy consistent with a myeloproliferative neoplasm (MPN) with grade 2 reticular fibrosis. Molecular mutation testing on the bone marrow confirmed a JAK2V617F mutation in 12% of DNA analyzed. The patient had mild hepatomegaly and splenomegaly (14cm x6.6cm) at time of initial visit. A diagnosis of primary myelofibrosis was established with a DIPSS score of 1 (intermediate -1) placing estimated survival at 80 months. Due to low risk disease and absence of symptoms, the patient was observed. In May 2018 the spleen rapidly increased in size from 15 to 24cm. He further progressed with early satiety, fatigue and diaphoresis in September 2018 leading to treatment initiation with Ruxolitinib 20mg twice a day.

The patient presented to the emergency room (ER) in November 2018 with hemoptysis and miliary pattern of pulmonary infiltrate on chest x-ray and chest computed tomography (CT) [Figure 1]. Respiratory acid-fast bacillus (AFB) culture and smear was positive for mycobacterium tuberculosis (TB) and QuantiFERON gold was positive, establishing a diagnosis of pulmonary TB. Ruxolitinib was discontinued and RIPE + vitamin B6 therapy was started in November 2018. RIPE therapy, or 4 drug TB therapy, consists of rifampin, isoniazid, pyrazinamide, and ethambutol. [1] The patient presented to the ER again in January 2019 with neck pain and fever of 100.2F. Magnetic resonance imaging (MRI) demonstrated a pattern of innumerable punctate enhancing lesions through

cerebellum and cervical spine concerning for miliary spread of TB to the central nervous system (CNS) [Figure 2]. Cerebrospinal fluid (CSF) had high protein and lymphocyte predominate differential. AFB culture and smear of the CSF was negative; therefore, a brain biopsy was deferred. The patient continued RIPE therapy for a total of 1 year with improvement of CNS lesions. Since holding ruxolitinib in November 2018 and treatment of TB to resolution, the patient has not had additional therapy for myelofibrosis. He currently has stable leukocytosis (30 K/μL), normocytic anemia (13 g/dL), and thrombocytosis (600 K/μL). His spleen, as of October 2020, remains stable at 20cm without symptoms of early satiety, weight loss or pain. He is currently on observation and aspirin 81mg daily for prophylactic anticoagulation.

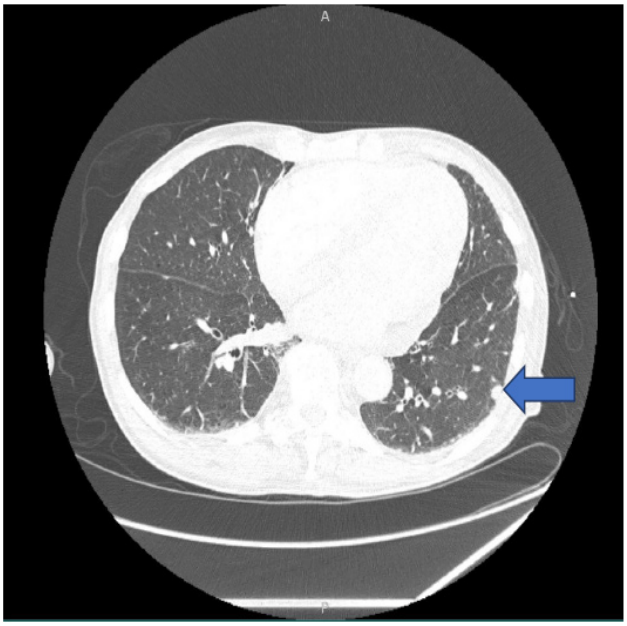

Fig1. *Chest CT, Mycobacterium Tuberculosis*

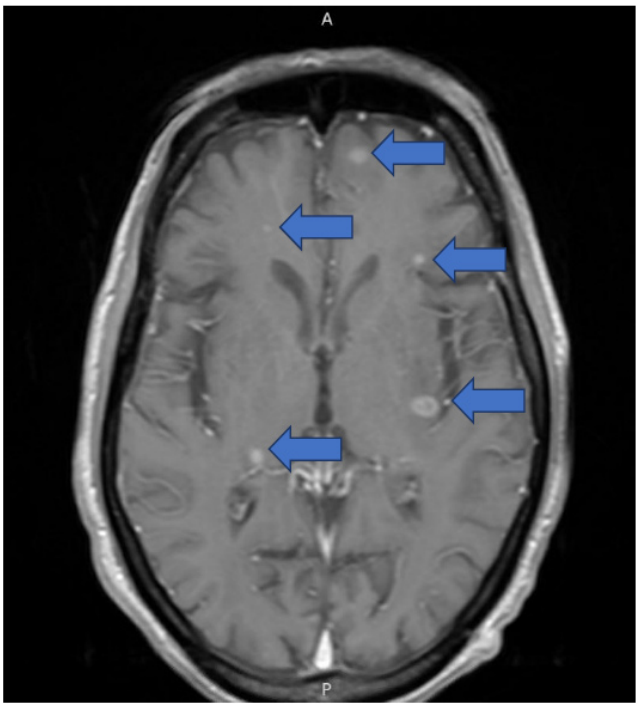

Fig2. *Brain MRI, Mycobacterium Tuberculosis*

Discussion

Primary myelofibrosis is a myeloproliferative neoplasm (MPN) characterized by bone marrow fibrosis presenting with cytopenias, abnormal cytokine expression with constitutional B symptoms, and splenomegaly associated with abdominal pain, early satiety, and weight loss. Activation of the JAK2 cellular signaling pathway is recognized as a pathway of increased levels of circulating proinflammatory cytokines in primary myelofibrosis, though this cellular signaling pathway is not completely understood. [2] Ruxolitinib is an oral JAK2 inhibitor targeting both JAK1 and JAK2 for treatment of myelofibrosis. [3, 4] Treatment with ruxolitinib attenuates cytokine signaling resulting in antiproliferative and antiapoptotic effects. FDA approval was based on patient quality of life improvements due to reduced spleen size and resolution of constitutional symptoms. The most common adverse reactions of this therapy (>10% incidence) are anemia, thrombocytopenia, bruising, dizziness, and headache.[4]

There was no increased risk of TB reported from the original ruxolitinib clinical trials. [5] The first report in the literature was 1 year following the FDA approval in 2011 in a patient receiving treatment with ruxolitinib for primary myelofibrosis, presenting with disseminated TB while on the COMFORT-II Phase 3 study. [6] The safety analysis of the COMFORT-II study eventually reported 1 patient with TB in the ruxolitinib arm. [7] This first case has been followed by 13 English language case reports of TB during ruxolitinib therapy [Table 1]. Most patients in these case reports were on ruxolitinib 20mg twice daily dosing for initial therapy of myelofibrosis. The median time from starting ruxolitinib to diagnosis of TB was 24 weeks. Most patients presented with either disseminated disease or lymphadenitis and were treated with 4 drug TB therapy. There are three TB related deaths reported in the case reports. In addition, there is a case report of mycobacterium avium in a polycythemia vera patient treated with ruxolitinib who died of related pulmonary complications.[8] Of note, no case reports were identified of mycobacterium infections among patients on ruxolitinib for graft versus host disease after allogeneic stem cell transplant and a recent study found no treatment effect on lung function after transplant.[9]

Any impairment in cell-mediated immunity may result in active TB. The risk of opportunistic infections including TB is increasing in developed countries due to increasing use of targeted agents with immune-modulating effects.[22] An increased risk of infection is noted as a possible side effect of ruxolitinib, related to decreased Th1 response and decreased production of interferon gamma.[23] Interferon gamma and tumor necrosis factor alpha are cytokines with critical roles in protective immunity against mycobacterium TB infection and reactivation.[24] Ruxolitinib also impairs dendritic cell development and function, including production of IL-12 which are involved in immune response to mycobacterium TB.[25, 26] There is a marked decrease in T-regulatory cells during treatment with ruxolitinib.[27] These immune side effects secondary to therapy provide an etiology for increased risk of opportunistic infection. Case reports suggests the sensitivity of serological tests may be impaired by ruxolitinib therapy, including a patient with two negative QuantiFERON gold tests despite active infection.[12]

MPNs are a hyperinflammatory state and associated with deregulation of immune homeostasis. Infections are a leading cause of morbidity and death in MPNs. [28] In addition to TB, there are reports of other opportunistic infections in patients treated with ruxolitinib including Cryptococcus neoformans, Toxoplasmosis, Pneumocystis jiroveci, progressive multifocal leukoencephalopathy, and Hepatitis B virus. [29-33] Given durable immunosuppression demonstrated by ruxolitinib, prescribers are challenged with long-term treatment related decisions regarding prophylaxis and monitoring for varicella zoster, Hepatitis B reactivation, and latent mycobacterial infections.[34] Authors have suggested screening for latent TB with tuberculin skin test or QuantiFERON gold and routine chest Xray.[34, 35] Reactivation of TB has been reported with other JAK receptor therapies including tofacitinib and baricitinib.[36, 37] Interestingly, imatinib, a tyrosine kinase (TKI) targeting agent used to treat other MPNs, has shown activity against drug resistant TB in mouse models.[38] Furthermore, there is report of using ruxolitinib to treat severe steroid-refractory neuro-tuberculosis paradoxical inflammatory reaction in a patient without myeloproliferative neoplasm.[39]

Table1. *Summary of Case Reports in Literature Review*

Diagnosis	Ruxolitinib Dose	Ruxolitinib duration prior to TB	Presentation of TB	Treatment and Outcome
Primary Myelofibrosis[10]	20mg BID	40 weeks	Disseminated	Ruxolitinib tapered over 4 months while treating with 4 drug TB therapy 5 months, death due to post-operative complication
Primary Myelofibrosis[11]	20mg BID	12 weeks	Pulmonary	Ruxolitinib stopped, 4 drug TB therapy
Secondary Myelofibrosis (PV) [12]	20 mg BID	16 weeks	Lymphadenitis	Ruxolitinib held, 4 drug TB therapy, restarted Ruxolitinib after 6 months TB therapy completed followed by prophylactic isoniazid
Primary Myelofibrosis[13]	20 mg BID	9 weeks	Disseminated	Ruxolitinib held, 4-drug TB therapy for 9 months. Restarted Ruxolitinib after 4 months of TB treatment with improvement in B symptoms
Primary Myelofibrosis [14]	20mg BID	12 weeks	Disseminated	Ruxolitinib stopped, 4 drug TB therapy, death 3 months after TB reactivation diagnosis
Primary Myelofibrosis[8]	15mg BID	19.4 weeks	Disseminated	Ruxolitinib stopped, TB therapy (agents unknown), death 3 months after TB diagnosis
Primary Myelofibrosis[15]	Not reported	Not reported	Lymphadenitis	Ruxolitinib stopped, 4 drug TB therapy
Primary Myelofibrosis[16]	20mg BID	24 weeks	Lymphadenitis	Ruxolitinib stopped 4 drug TB therapy for 6 months, restarted Ruxolitinib without benefit for myelofibrosis
Primary Myelofibrosis[17]	20mg BID	16 weeks	Pulmonary	Ruxolitinib stopped, TB therapy with isoniazid, rifampicin, ethambutol, and levofloxacin for 12 months, retreated with Ruxolitinib
Primary Myelofibrosis[17]	20mg BID	8 weeks	Disseminated	Continued Ruxolitinib, TB therapy with isoniazid, levofloxacin, rifapentine, and amikacin for 12 months with refractory and progressive TB, amikacin replaced with ethambutol
Polycythemia Vera[18]	20mg BID	28 weeks	Peritonitis	Ruxolitinib changed to hydroxyurea, 4 drug TB therapy for 6 months, continued hydroxyurea
Primary Myelofibrosis[19]	20mg BID	16 weeks	Pulmonary	Ruxolitinib stopped, 4 drug TB therapy
Primary Myelofibrosis[20]	15mg BID	84 weeks	Lymphadenitis	Ruxolitinib continued, 4 drug TB therapy for 12 months
Primary Myelofibrosis[21]	Not reported	Not reported	Disseminated	Change in Ruxolitinib not reported, 4 drug TB therapy

**4 drug TB therapy = rifampin, isoniazid, pyrazinamide, ethambutol; BID = twice a day*

Conclusion

This case report and review of the literature highlights occurrence of TB in patients treated with ruxolitinib. While occurrence of TB is rare, immunosuppressive and immunomodulatory effects of ruxolitinib pose a special problem for the incidence of this infection in an already vulnerable patient population.[40] Consideration for pretreatment screening should be strongly considered for patients from areas endemic for mycobacterium infections or with social risk factors. [10, 41]

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