Ruxolitinib-associated tuberculosis – A rare complication of a novel drug!

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ABSTRACT

Primary myelofibrosis (PMF) is a myeloproliferative disorder characterized by bone marrow fibrosis, abnormal cytokine expression, abnormal proliferation of megakaryocytes, and splenomegaly. Ruxolitinib (INCB018424) is a novel non-specific Janus-like kinase inhibitor available for the management of PMF as it reduces spleen size and gives significant symptomatic relief. Very few case reports are available depicting opportunistic infections associated with this drug. We present a case of 35-year-old female - A known case of PMF on follow-up since 7 years. She was started on ruxolitinib in view of symptomatic progressive splenomegaly and weight loss. She was asymptomatic till 4th month of starting drug when she developed fever, body ache, and right axillary swelling. The right axillary lymph node biopsy revealed necrotizing granulomatous lymphadenopathy of tuberculous etiology (acid-fast bacilli [AFB] positive). X-ray of the chest was normal. She was started on antituberculosis (TB) treatment, and ruxolitinib was also continued. Patient is currently asymptomatic and has gained weight. She is on continuation phase of anti-TB treatment.

KEY WORDS: Primary Myelofibrosis; Ruxolitinib; Tuberculosis

INTRODUCTION

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm characterized by abnormal proliferation of megakaryocytes, bone marrow fibrosis, and extramedullary hematopoiesis.[1] The 2008 World Health Organization definition of PMF includes Janus-like kinase (JAK) JAK2V617F, CALR, or MPL (W515) mutations as a major diagnostic criterion.[2] Most of the patients present with constitutional symptoms such as fatigue, fever, weight loss, and abdominal pain.[4] Although pathogenesis is not fully understood, many cytokines play an important part - mainly transforming growth factor beta, platelet-derived growth factor, and interleukin 1 (IL-1), etc. Mutated JAK2 leads to upregulation of these cytokines.[5,6] Bone marrow transplant is the only curative treatment for the disease, and extensive workup is going on for targeted therapy. One of such targeted drugs that inhibit both JAK1 and JAK2 are ruxolitinib. This drug is approved for PMF patients and has shown to reduce constitutional symptoms and spleen size.[7] Few case reports are published related to opportunistic infections associated with ruxolitinib as it leads to immunosuppression.[3,4,8] To the best of our knowledge, very few clinical trials have shown increased risk of tuberculosis (TB) with this drug, and only sporadic case reports are available till date.[9] We hereby report a rare case of TB associated with this novel drug.

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CASE REPORT

A 35-year-old female presented in the year 2007 with fever and mild splenomegaly. She was investigated and diagnosed as PMF and was found to have mutated CALR (Type 1) gene in 2015. As she was asymptomatic from PMF point of view, she was observed for around 7 years. Then, as she had occasional pain in the left hypochondriac region due to splenomegaly, she was started on lenalidomide and prednisolone in February 2014. From July 2015, patient developed fever and had

H1N1 positive pneumonia. High-resolution computerized tomography of the chest was suggestive of interstitial pneumonitis of viral etiology. She was admitted in intensive care unit and received antivirals and antibiotics and improved. Then, patient had symptomatic progressive splenomegaly and weight loss. For this, she was started on ruxolitinib 20 mg BID on 1/8/2015. She was asymptomatic till late November 2015 when she developed fever, body ache, and right axillary swelling. Patient underwent right axillary lymph node biopsy that revealed necrotizing granulomatous lymphadenopathy of tuberculous etiology with AFB-positive (Figure 1). X-ray of the chest was normal. She is on anti-TB treatment since December 2015, and ruxolitinib is also continued. Patient has gained weight and is currently asymptomatic. She is on continuation phase of anti-TB treatment from February 2016. In view of progression of disease and increased Dynamic International Prognostication Scoring System score, she was referred to outside center for matched allogeneic bone marrow transplant and is now clinically stable in post-transplant period.

DISCUSSION

PMF is a distinct breakpoint cluster region-ABL negative myeloproliferative disorder with most of the patients showing one of the mutations out of JAK2, CALR, or MPL mutations.[2] Very few patients are negative for all these mutations. No specific drug therapy was available until discovery of JAK inhibitors such as ruxolitinib and patients were treated symptomatically using steroids, immunomodulator drugs, or erythropoietin. Ruxolitinib is found to relieve symptoms related to splenomegaly and is shown to reduce spleen size.[9] The drug acts by inhibiting JAK1 and JAK2 that leads to immunosuppression. It attenuates the T-helper cell Type 1 response causing suppression of cytokines such as IL-1, IL-6, interferon-γ (INF), and tumor necrosis factor-α (TNF).[4] It is also shown to reduce dendritic cell function and IL-12 production.[4] This immunosuppression plays a nidus for new opportunistic infections or reactivation of latent infections.

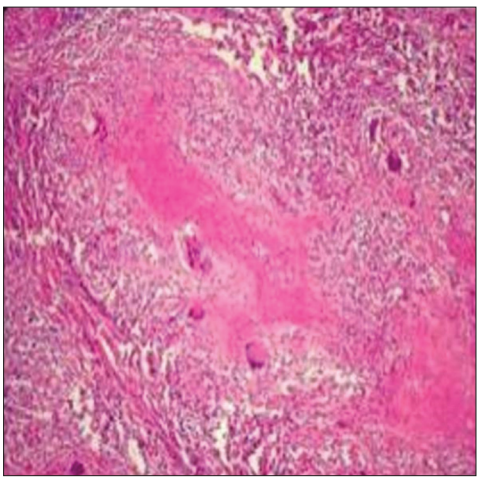

Figure 1: Lymph node biopsy showing caseous necrosis, Langhans giant cells, and epithelioid cells

Mycobacterium TB causes activation of macrophages and dendritic cells which lead to the production of various cytokines such as TNF-α, IL-1, IL-6, IL-15, and mainly IL-12. IL-12 along with other cytokines, through JAK1 and JAK2 pathway, regulates production INF-γ - A key cytokine to give protective immunity against *Mycobacterium* TB. INF-γ activated macrophages produce bactericidal superoxides that limit the growth of ingested organism. Ruxolitinib causes disruption of this protective mechanism and thus leads to TB infection or activation of latent infection.[3]

Our case was an old known case of PMF and was stable for many years. She had progressive symptoms but never had TB disease in the past. The infection occurred after starting ruxolitinib. Very few similar such cases are reported till date. TB lymphadenitis was reported in two patients of Korean study of ruxolitinib in PMF.[10] In COMFORT-II study that compared ruxolitinib with best available therapy in PMF, two patients (1.4%) in ruxolitinib arm were diagnosed as TB.[12] Hopman et al. also reported disseminated TB associated with ruxolitinib.[6] Cases of cryptococcosis,[8] hepatitis B,[11] and toxoplasmosis[13] associated with ruxolitinib are also reported in literature.

Although the cases are few and no epidemiological studies are available, the above observations hint toward likely association of increased risk of TB and other opportunistic infections in PMF patients treated with ruxolitinib. Thus, large-scale data are necessary to prove above hypothesis. Furthermore, routine patient screening for latent MTB infection may be considered in PMF patients before starting this drug, especially in countries like India where this infectious disease is rampant.

CONCLUSION

Our case highlights the importance of vigilant follow-up of patients on ruxolitinib and to look for unexpected complications such as opportunistic infections. The cause of such complications may be reactivation of latent infections due to immunosuppression by this novel drug. Although there is no consensus regarding the continuation of ruxolitinib in these cases, we continued the drug and patient is responding to the same. Furthermore, we suggest routine screening for latent TB infection before starting JAK inhibitors.

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