Case Report

Tuberculosis reactivation related with ruxolitinib in a patient with primary myelofibrosis

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Abstract

Primary myelofibrosis (PMF) is a clonal stem cell disease, characterized by bone marrow fibrosis. Ruxolitinib is a selective inhibitor of JAK-1 and JAK-2 used to treat PMF. Its mechanism of action is based on the reduction of signal transduction and cytokine levels; including IL-6 and tumor necrosis factor alpha. Increased infection risk related to Ruxolitinib is rarely reported. Here we describe a case of tuberculosis infection reactivation in a female patient treated with Ruxolitinib. During the treatment, she complained of night sweats, weight loss and enlarged mass in the neck. Excisional mass biopsy revealed a necrotizing granulomatous lymphadenitis. QuantiFERON-TB and PPD tests were not able to diagnose the tuberculosis infection. Therapy with Ruxolitinib was interrupted due to possible immunosuppressive effects and the patient was treated with the standard antituberculosis regimen. After six months, the patient’s symptoms had resolved and there was no lymphadenopathy. In conclusion, it is important to assess the risk of tuberculosis activation before Ruxolitinib treatment. In addition, the diagnosis of tuberculosis using QuantiFERON-TB and PPD may be misleading in patients treated with Ruxolitinib.

Key words: Primary myelofibrosis; ruxolitinib; tuberculosis; infection; JAK-2 inhibitor.

J Infect Dev Ctries 2018; 12(10):926-928. doi:10.3855/jidc.9993

(Received 28 November 2017 – Accepted 24 July 2018)

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Introduction

Primary myelofibrosis (PMF) is a clonal stem cell disease, characterized by bone marrow fibrosis, atypical hyperplasia, abnormal cytokine expression, splenomegaly and anemia. The cause of the disease is still unknown, but a mutation in JAK2 V617F occurs in 50-60% of patients. Ruxolitinib is a selective inhibitor of JAK-1 and JAK-2. Its mechanism of action is a reduction in signal transduction and cytokine levels; including IL-6, tumor necrosis factor alpha (TNF-α). It reduces constitutional symptoms and splenomegaly. Anemia and thrombocytopenia are more common in the early phases of therapy. Most common non-hematological side effects are ecchymosis, headache, and dizziness. Increased infection risk related Ruxolitinib is rarely reported. Here we describe a case of tuberculosis infection in a patient treated with Ruxolitinib.

Case presentation

A 52-years-old female was diagnosed with PMF (DIPSS plus intermediate-2 risk) in 2012. Hydroxyurea was administered. After three years, hydroxyurea was discontinued owing to an increase in spleen size. Ruxolitinib treatment was started at 20 mg twice a day. After 6 months of Ruxolitinib treatment, we observed a reduction in spleen size of more than 50%. 8 months following the introduction of Ruxolitinib, the patient complained of night sweats, weight loss and enlarged mass in the neck. Physical examination showed pallor, lymphadenopathy (1×1.5 cm on the right side of the neck) and splenomegaly. Laboratory test results revealed Hb 7.9 g/dL, white blood cell (WBC) 5500 cells/mm³, neutrophils 3800 cells/mm³, platelets 97000 cells/mm³, total and direct bilirubin 1,16/0.42 mg/dL, lactate dehydrogenase (LDH) 513 IU, albumin 4.3 g/dL, erythrocyte sedimentation rate (ESR) 136 mm/h and C-reactive protein (CRP) 27.3 mg/dL. Neck ultrasonography revealed a 38×29 mm lymphoid mass in the right cervical area. The excision and biopsy of the mass revealed necrotizing granulomatous lymphadenitis (Figure 1). Immunohistochemical evaluation (Ziehl-Neelsen staining) and a PCR test did not support a tuberculosis infection suspect. The
QuantiFERON-TB gold test was also negative. However the purified protein derivative (ppd) test gave a reading of 12 mm. The patient was diagnosed with tuberculosis lymphadenitis based on the clinical and pathological findings. Ruxolitinib was discounted due to the possible immunosuppressive effects and the patient was treated with antituberculosis regimen including isoniazid, rifampicin, pyrazinamide and ethambutol. After six months, the patient’s symptoms resolved and there was no lymphadenopathy. The spleen size had increased during the 6 months without Ruxolitinib treatment. After the Ruxolitinib therapy was restarted, we observed again splenomegaly and the symptoms related to PMF did not reduce.

Discussion

The JAK/STAT signal metabolic pathway is one of the systems that play an important role in autoimmunity, the immune system and hematopoiesis [1]. JAK-1 and JAK-2 inhibitors reduce the Th1 response and the levels of IL-1, IL-6, TNF-α and gamma IFN (IFN-γ) which all play a role in myelofibrosis-associated constitutional symptoms [2]. The most frequently observed side effect of Ruxolitinib is hematological toxicity. Infectious complications have rarely been observed in other literature. However, hepatitis B infection, toxoplasma retinitis, tuberculosis infection, and simian virus-40 induced progressive multifocal leukoencephalopathy have been identified in several case series after Ruxolitinib treatment [3-7]. Only the 5% of healthy individuals who have contact with patients with active tuberculosis, develop the disease. Mycobacterium tuberculosis is inactive in granulomas (latent state) in the 95% of healthy individuals, owing to immune system activation. However, if patients use biological drugs such as TNF blockers, interleukin antagonists, or JAK inhibitors, a latent tuberculosis infection may become active. In the literature, Colomba et al. (2012) published the first report of tuberculosis reactivation during Ruxolitinib treatment. IFN-γ and TNF-α cytokines give protective immunity against tuberculosis. Tuberculosis infection leads to the activation of alveolar macrophages with the production of cytokines (IL-12, IFN-γ, IL-1, 6, 5, 12, 18). These cytokines prevent the infection spread. Tuberculosis infection risk may increase as a result of Ruxolitinib therapy, because these cytokines’ levels downregulates.

Diagnosis of tuberculosis infection is based on the QuantiFERON test which measures the IFN-γ level in the patient’s serum. In the normal population, the sensitivity and specificity is 90% and 95-98% respectively. Quantiferon test-negative cases have been reported in patients treated with Ruxolitinib. This may be due to the reduced cytokine levels [9]. Based on these findings, it can be affirmed that during Ruxolitinib treatment, the sensitivity of serological tests for tuberculosis infection is reduced. In such cases, Mycobacterium tuberculosis can be identified by culture of the lymph node. According to our case experience and literature knowledge, tuberculosis infection is observed during Ruxolitinib treatment; this drug should be discontinued and standard tuberculosis treatment must be started. At the end of the standard treatment, it is recommended to restart the treatment with Ruxolitinib using secondary prophylaxis with Isoniazid [10].

Latent tuberculosis risks are still high in Turkey. It is important to assess the tuberculosis activation risk before to start a Ruxolitinib treatment, because it may increase the risk of infection. In addition, the diagnosis of tuberculosis by using QuantiFERON and PPD skin test may be misleading in patients treated with Ruxolitinib, therefore, microbiological and pathological data may be more useful in this case.

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**Conflict of interests:** No conflict of interests is declared.