Case Report
A myelofibrosis case that develops mycobacterial infection after ruxolitinib treatment

Umit Yavuz Malkan, Ibrahim Celalettin Haznedaroglu

Department of Hematology, School of Medicine, Hacettepe University, Ankara, Turkey

Received October 11, 2016; Accepted February 16, 2017; Epub April 15, 2017; Published April 30, 2017

Abstract: Ruxolitinib is a novel therapeutic agent which is being used in the treatment of myelofibrosis. In the literature, there are reports of opportunistic infections along with tuberculosis during ruxolitinib treatment. Herein, we aimed to report a post-polycythemic myelofibrosis case that developed mycobacterial infection after ruxolitinib treatment. A 64 years old man was diagnosed as polycythemia vera 27 years ago. He was diagnosed as post-polycythemic myelofibrosis in 2002. He was given hydroxycarbamide and interferon treatments, however ruxolitinib treatment was started in July 2015 because of spleen enlargement and constitutional symptoms. Ruxolitinib was started with a dose of 2×5 mg and the dose gradually increased to 2×20 mg by September 2015. His constitutional symptoms decreased and cachexia improved by January 2016. However he started to have fever attacks. Investigations revealed no origin for fever. The quantiferon test was resulted positive in May 2016. Tuberculosis PCR test was negative. However, ADA level was found to be increased in cerebrospinal fluid. General condition of the patient deteriorated rapidly and he was lost in June 2016. Afterwards “mycobacterium tuberculosis complex” was detected in our patient’s culture sample. Ruxolitinib has serious effects on immune system. To conclude, patients who are given ruxolitinib should be closely followed-up especially in the first months of treatment and benefits and prophylactic use of antivirals and antibiotics should be investigated in future studies.

Keywords: Ruxolitinib, mycobacterial infection, myelofibrosis

Introduction

Tuberculosis is a common infectious disease caused by various strains of mycobacteria, generally Mycobacterium tuberculosis. Mycobacterium typically affects the lungs, but can also spread to other parts of the body [1]. Mycobacterium tuberculosis complex refers to a genetically related group of Mycobacterium species that can cause tuberculosis. Myelofibrosis is a myeloproliferative disease that characterizes with histological megakaryocyte proliferation, cytokine dysregulation and bone marrow fibrosis [2]. The underlying pathogenesis of myelofibrosis is still not fully understood. A mutation in the tyrosine-protein kinase Janus-activated kinase 2 (JAK2) is thought to result in up regulation of proinflammatory cytokines [3]. Ruxolitinib is a novel therapeutic agent which is being used in the treatment of myelofibrosis. Ruxolitinib works by inhibiting JAK1 and JAK2, resulting in immunosuppression. Ruxolitinib decreases the T-helper cell type 1 (Th 1) response and down regulates interleukin-1, interleukin-6, interferon-γ, and tumor necrosis factor-α [4]. Recently it has been shown that ruxolitinib impairs dendritic cell development and function, including production of interleukin-12 by dendritic cells [5]. Ruxolitinib is an effective treatment for myelofibrosis, it reduces the spleen size and constitutional symptoms [3]. In the literature, there are reports of opportunistic infections along with tuberculosis during ruxolitinib treatment [6]. Herein, we aimed to report a post-polycythemic myelofibrosis case that developed mycobacterial infection after ruxolitinib treatment.

Case report

All of the ethical considerations were strictly handled in accordance with the Helsinki Declaration. As a standard of care/action of the hospitals of Hacettepe Medical School, the patient gave written and informed consent at
Mycobacterial infection after ruxolitinib treatment

Figure 1. Cerebellum involvement of the patient in T2 cranial MR.

the time of hospitalization. 64 years old man was diagnosed as polycythemia vera 27 years ago. He had been given acetylsalicylic acid and he was followed up with repetitive phlebotomies. In 2002, bone marrow investigation revealed an increase in reticulin fibers and myeloid/erythroid ratio. He was diagnosed as post-polycythemic myelofibrosis. He was given calcitriol treatment. In 2002, abdominal ultrasonography revealed his spleen size as 23 cm. In 2014, his white blood cell count was detected as 39.2×10^3/µl, therefore he was investigated for blastic transformation. After ruling out blastic transformation, hydroxycarbamide treatment was started for our patient. In February 2015, his laboratory tests were resulted as hemoglobin 13.1 gr/dl, white blood cell 16.7×10^3/µl, and platelet 205×10^3/µl. He had the complaints of early satiation and dyspnea. His physical examination revealed a plethoric face, his liver and spleen were palpable under costa with 6 cm and 8 cm, respectively. Bone marrow investigation revealed a hypocellular bone marrow with an increase in reticulin fibers. Therefore, pegylated-interferon treatment was started. He had cachexia and poor performance status; so he was not considered as a bone marrow transplantation candidate. He was given hydroxycarbamide and interferon treatments however ruxolitinib treatment was started in July 2015 because of spleen enlargement and constitutional symptoms. Ruxolitinib was started with a dose of 2×5 mg and the dose gradually increased to 2×20 mg by September 2015. Laboratory tests in January 2016 were resulted as hemoglobin 9.7 gr/dl, white blood cell 5.7×10^3/µl, and platelet 245×10^3/µl. His constitutional symptoms decreased and cachexia improved by January 2016. However he started to have fever attacks. These attacks had occurred 3 or 4 times per day and repeated for every 15 days as cycles. His fever attacks reached to 39 degree centigrade. In April 2016, he was hospitalized in order to clarify the reason for these fever attacks. His laboratory tests in April 2016 were resulted as hemoglobin 7.4 gr/dl, white blood cell 4.9×10^3/µl, and platelet 186×10^3/µl. Investigations revealed no origin for fever. Cranial MR was performed in order to clarify hyponatremia and it was resulted as “intraparenchymal mass in left cerebellum, diffuse contrast enhancement in leptomeninges, leptomeningeal carcinomatosis. Infections should be considered in differential diagnosis” (Figure 1). Tests for brucella and syphilis were negative, but quantiferon test was dramatic positive in May 2016. Tuberculosis PCR test was negative. However, ADA level was found to be increased in cerebrospinal fluid. Suddenly, aphasia and confusion were developed in our patient, so intracranial operation could not be performed. General condition of the patient deteriorated rapidly and he was lost in June 2016. Afterwards “mycobacterium tuberculosis complex” was detected in our patient’s culture sample.

Discussion

Ruxolitinib was shown to be very effective for reducing spleen size and constitutional symptoms of myelofibrosis cases [3]. Similarly, constitutional symptoms and spleen size were reduced in our patient by ruxolitinib treatment. However, ruxolitinib has serious effects on immune system. In myelofibrosis cases that are given ruxolitinib, the T helper cell type 1 response and cytokines such as IFN-γ and TNF-α decrease because of the inhibition of JAK-STAT signaling [7]. IFN-γ and TNF-α play an important role in control of tuberculosis infection. Also, TNF-α is very important in T cell function, macrophage activation, and granuloma formation [7]. As a result reactivation or dissemination of infections, particularly atypical
Mycobacterial infection after ruxolitinib treatment

Table 1. Summary of previous reports who were given ruxolitinib and developed tuberculosis infection

<table>
<thead>
<tr>
<th>Age/Gender</th>
<th>Important Clinical Feature</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>78/Female</td>
<td>Use of rifampin for treatment of disseminated tuberculosis in a patient with primary myelofibrosis on ruxolitinib</td>
<td>[13]</td>
</tr>
<tr>
<td>72/Male</td>
<td>A myelofibrosis case died from complications of fulminant disease after ruxolitinib treatment</td>
<td>[14]</td>
</tr>
<tr>
<td>68/Male</td>
<td>A myelofibrosis case died from pulmonary tuberculosis after ruxolitinib treatment</td>
<td>[14]</td>
</tr>
<tr>
<td>62/Male</td>
<td>Disseminated tuberculosis associated with ruxolitinib in a primary myelofibrosis case</td>
<td>[15]</td>
</tr>
<tr>
<td>65/Female</td>
<td>A myelofibrosis case that developed an extrapulmonary TB while on ruxolitinib treatment</td>
<td>[16]</td>
</tr>
<tr>
<td>62/Male</td>
<td>Pulmonary tuberculosis reactivation following ruxolitinib treatment in a patient with primary myelofibrosis</td>
<td>[17]</td>
</tr>
<tr>
<td>78/Female</td>
<td>Ruxolitinib Associated Tuberculosis Presenting as a Neck Lump</td>
<td>[18]</td>
</tr>
<tr>
<td>N/A* /Male</td>
<td>Disseminated tuberculosis in a primary myelofibrosis patient treated with ruxolitinib</td>
<td>[2]</td>
</tr>
<tr>
<td>69/Male</td>
<td>Reactivation of Pulmonary Tuberculosis following Treatment of Myelofibrosis with Ruxolitinib</td>
<td>[8]</td>
</tr>
</tbody>
</table>

*N/A: not applicable.

bacterial, mycobacterial, fungal, and viral infections may be seen in patients who are given ruxolitinib. In the literature, there are previous reports regarding the side effects of ruxolitinib treatment such as progressive multifocal leukoencephalopathy, toxoplasmosis retinitis, cryptococcal pneumonia, herpes zoster infection and reactivation of hepatitis B [8-11]. These side effects develop because of immunosuppressive effect of ruxolitinib. Also, ruxolitinib is blamed for tuberculosis infections. In the literature there are a few case reports regarding the tuberculosis infections in myelofibrosis patients who were given ruxolitinib (Table 1) [2, 7, 12-17]. The average time between the initiation of ruxolitinib and beginning of tuberculosis symptoms is approximately 2-4 months [17]. Similarly, the episode between the initiation of ruxolitinib and the onset of fever attacks in our patient which were later considered secondary to mycobacterium infection is approximately 4 months. Although our patient had ADA elevation and quantiferon positivity; mycobacterium proliferation in culture could not be shown while he was alive. Intracranial sampling could not be performed because the general condition of our patient had deteriorated rapidly. The evidence of mycobacterium in culture could be detected after the loss of the patient. Exact diagnosis could not be made by MR test although there was a suspicious signs. In the literature, there are reports that suggest prophylactic treatment with isoniazid during ruxolitinib treatment although there is no sign of reactivation of tuberculosis [15]. Another study proposes routine antiviral and antibiotic prophylactic treatments during ruxolitinib treatment [18]. Some other authors suggest screening for tuberculosis in endemic areas before ruxolitinib treatment or directly starting antituberculosis treatment if there is a risk factor in the patient [14]. Our patient is one of the few myelofibrosis cases that developed tuberculosis infection during ruxolitinib treatment. Differently from the previous reports, our patient had a tuberculosis infection that led to a fast developing cranial intraparenchymal mass after fever attacks. To conclude, patients who are given ruxolitinib should be closely followed-up especially in the first months of treatment and benefits and prophylactic use of antivirals and antibiotics should be investigated in future studies.

Disclosure of conflict of interest

None.

Address correspondence to: Umit Yavuz Malkan, Department of Hematology, School of Medicine, Hacettepe University, 06100, Ankara, Turkey. Tel: +90-5327780087; Fax: +90-3123051614; E-mail: umitmalkan@hotmail.com

References


Mycobacterial infection after ruxolitinib treatment


