Case Report

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Varicella Zoster Infection Associated with Pharmacological JAK-STAT Inhibition via Ruxolitinib in Myeloproliferative Diseases

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Abstract

Ruxolitinib phosphate is an inhibitor drug of the JAK family of protein kinases. The results from two Phase III studies in myelofibrosis (COMFORT-I, COMFORT-II) demonstrate the effectiveness of Ruxolitinib in patients with primary myelofibrosis (MF), post-polycythemia vera myelofibrosis (PV-MF) and post-essential thrombocythemia myelofibrosis (ET-MF). On the other hand, Ruxolitinib affects several cytokines (IL1, IL6 and TNF-α) and other immune processes (dendritic cells function and T-cell response) and has been linked to increased incidence of opportunistic and non-opportunistic infections. The JAK-inhibitor Ruxolitinib affects the dendritic cell differentiation, phenotype, and function leading to impaired T-cell activation. Varicella zoster virus (VZV) infections are usually considered as having benign clinical courses. However, it sometimes can cause potentially fatal or long term disabling outcomes, including bacterial superinfections, coagulopathies, and central nervous system manifestations. Despite the low mortality rate in the immunocompetent patients, in immunocompromised patients primary VZV infections can become life-threatening. In the literature, VZV infections related allogeneic bone marrow transplantation had also been presented. To our knowledge, there are no reported association between VZV and myeloproliferative disorders (MPD) other than the process of bone marrow transplantation. Here we describe the first cases with cutaneous manifestations of VZV infections, who receiving Ruxolitinib therapy for MPD.

Keywords: Varicella zoster; Infection; Myelofibrosis; Splenomegaly; Ruxolitinib; JAK2 inhibitor

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Introduction

Ruxolitinib phosphate (INCB018424 phosphate, INC424) is an inhibitor drug of the JAK family of protein kinases [1]. Ruxolitinib represents a novel, potent, and selective inhibitor of JAK1 and JAK2 with modest to marked selectivity against tyrosine kinase TYK2 and JAK3 leading to a novel, potent, and selective inhibition of JAK-STAT signal transduction system. Likewise, Ruxolitinib has high selectivity against a number of non-JAK kinases [2-5].

The results from two Phase III studies in myelofibrosis (COMFORT-I, COMFORT-II) demonstrate the effectiveness of Ruxolitinib in patients with primary myelofibrosis (MF), post-polycythemia vera myelofibrosis (PV-MF) and post-essential thrombocythemia myelofibrosis (ET-MF) [6-10]. The results of those studies had indicated significant differences in rates of ≥ 35% spleen volume reduction compared with either placebo or best available therapy (BAT) [6-10].

On the other hand, Ruxolitinib affects several cytokines (IL1, IL6, and TNF-α) and other immune processes (dendritic cells function and T-cell response) and has been linked to increased incidence of opportunistic and non-opportunistic infections [11]. The JAK-inhibitor Ruxolitinib affects the dendritic cell differentiation, phenotype, and function leading to impaired T-cell activation [12].

Varicella zoster virus (VZV) infections are usually considered as

having benign clinical courses. However, it sometimes can cause potentially fatal or long term disabling outcomes, including bacterial super infections, coagulopathies, and central nervous system manifestations [13,14]. Despite the low mortality rate in the immune-competent patients, in immune-compromised patients primary VZV infections can become life-threatening. In the literature, VZV infections related allogeneic bone marrow transplantation had also been presented [15,16].

To our knowledge, there are no reported association between VZV and myeloproliferative disorders (MPD) other than the process of bone marrow transplantation. Here we describe the first cases with cutaneous manifestations of VZV infections, who receiving Ruxolitinib therapy for MPD.

Case Reports

Case 1

A 51-year-old male patient with a 4 years history of polycythemia vera, who received hydroxiurea and acetyl salicylic acid (ASA) treatment, admitted to our hematology clinic with night sweats, weight loss, enlarging mass and pain in the left upper quadrant for three months. On admission, physical examination showed a hepatosplenomegaly. Laboratory test results revealed, RBC 7320000 cells/mm^3, Hb 16.4 g/dL, Hct 53.4%, WBC 7800 cells/mm^3 (N 69.6%, L 19.8%, M 4.3%), PLT 378000 cells/mm^3, corrected reticulocyte rate 1.7%, total and direct bilirubin 1.18/0.40 mg/dL, LDH 329 U/L, beta 2 microglobulin 2044 mg/L, erythrocyte sedimentation rate (ESR) 2 mm, C-reactive protein (CRP) 3 mg/dL and EPO<0.6 mIU/mL. Laboratory tests for hepatitis A-B-C, HIV, TORCH, EBV, brucella (Rose Bengal and Coombs), salmonella, ANA and Anti-dsDNA were negative. Peripheral blood smear showed characteristic teardrop poicilocytes, nucleated red cell and neutrophil with dysmorphic nucleus. Abdominal CT-scan showed hepatomegaly (208 mm) and splenomegaly (235 mm). Marrow aspiration revealed, hypercellular marrow with increased number of hypolobulary megacaryocytes. Marrow biopsy specimen showed Grade III reticulin fibrosis. JAK2 V617F mutation was positive in real-time PCR. The patient diagnosed as post-PV MF, according to International Working Group for Myeloproliferative Neoplasms Research and Treatment Criteria. Hydoxiurea and oral JAK2 inhibitor (Ruxolitinib) 2x20 mg p.o. treatment was initiated. During the sixth month of Ruxolitinib treatment clinical symptoms of the patient was improved and spleen size was reduced to 208 mm from 235 mm. In physical examination, a number of painful vesicular rash at left eyelid, supraorbital area and left half of the frontal scalp were detected (**Figure 1**). After dermatological examination, cutaneous manifestations were diagnosed as VZV infection, thus, Ruksolitib treatment was discontinued and antiviral treatment (Asiviral tablets 5x400 mg/day, Terra, Turkey) was initiated. After two weeks with antiviral treatment, painful vesicular lesions were disappeared (**Figure 2**) and the Ruxolitinib treatment was continued.

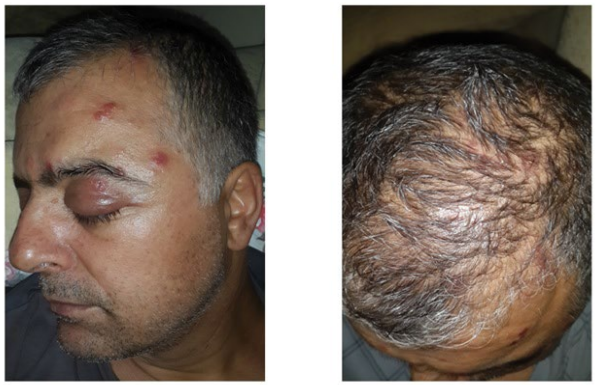

Figure 1 Painful vesicular rash at left eyelid, supraorbital area and left half of the frontal scalp.

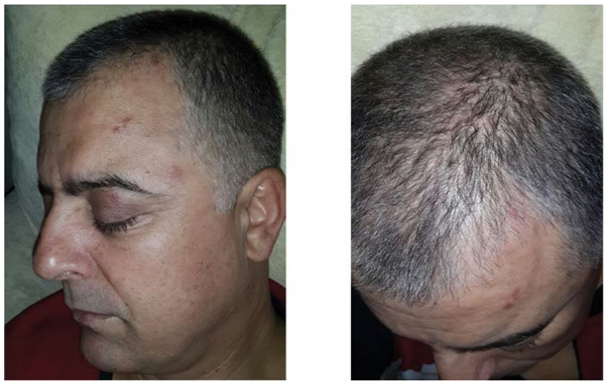

Figure 2 After anti-viral treatment, painful vesicular lesions disappeared.

Case 2

A 65-year-old female patient with a 16 year history of polycythemia vera, who received hydroxiurea and ASA treatment, admitted with night sweats, weight loss, enlarging mass and pain in the left upper quadrant and 1-2 packet/month transfusion required anemia for two months. On admission, physical examination showed a splenomegaly. Laboratory test results revealed, RBC 2990000 cells/mm^3, Hb 8.9 g/dL, Hct 27.9%, WBC 20990 cells/mm^3 (N 71%, L 12.6%, M 14.3%), PLT 503000 cells/mm^3, corrected retikulocyte rate 1%, total and direct bilirubin 0.94/0.36 mg/dL, LDH 1120 U/L, beta 2 microglobulin 2340 mg/L, ESR 2 mm, CRP 2.5 mg/dL and EPO 2.4 mIU/mL. Laboratory tests for hepatitis A-B-C, HIV, TORCH, EBV, brucella (Rose Bengal and Coombs), salmonella, ANA and Anti-dsDNA were negative. Peripheral blood smear showed characterictic teardrop poicilocytes, nucleated red cell and neutrophil with dysmorphic nucleus. Abdominal CT-scan showed splenomegaly (277 mm). Marrow aspiration revealed hypercellular marrow. Marrow biopsy specimen showed Grade III reticulin fibrosis. JAK2 V617F mutation was positive in real-time PCR. The patient diagnosed as post-PV MF and Ruxolitinib 2x20 mg p.o. was initiated. During the fourth month of Ruxolitinib treatment, clinical symptoms of the patient was improved, transfusion requirement and spleen size was reduced (277 mm to 210 mm). In physical examination, painful vesicular rashes at whole frontal area were detected. Cutaneous manifestations were diagnosed as VZV infection, thus, Ruksolitib treatment was discontinued and antiviral treatment (Asiviral tablets 5x400 mg/day, Terra, Turkey) was initiated. After two weeks with antiviral treatment, painful vesicular lesions were disappeared and the Ruxolitinib treatment was continued.

Case 3

A 55 year-old male patient admitted with itching, nosebleed and enlarging mass in left upper quadrant. His physical examination revealed splenomegaly. Laboratory tests revealed, Hb 19.3 gr/dl, hematocrit 59.3, WBC 14.2 × 10^3/μL, thrombocyte 656000/mm^3, LDH 792 U/L, total bilirubin 1.3 mg/dl, creatinine 1.2 mg/dl, bcr-abl (with PCR techic) negative, EPO 4 mIU/ml, sedimantation 2 mm/hour, CRP 1 mg/L corrected reticulocyte 1.1%. 85% neutrophil, lots of platelets was seen in blood film. HBsAg was pozitive. Abdominal ultrasonography revealed the spleen as 148 × 84 mm. Bone marrow aspiration and biopsy reported as "increased myeloid/eritroid ratio and hiperplasia of megacaryocytes, favors with chronic myeloid disease". He was diagnosed as polycythemia vera. He had Jak 2 mutation positive and patient was given cytoreductive treatment. He was followed with flebotomy, hydroxicarbamide and ASA treatment up 7 years. After 7 years, he still had need of flebotomy and his laboratory test were as; Hb 15.1 gr/dl, Htc 48.0, WBC 4.2 × 10^3/μL, thrombocyte 349.000/mm^3. He had no blast in blood film and his ECOG score was 1. He was decided to participate in Ruxolitinib study as polycythemia vera grade 2 patient. In physical examination, he had spleen size of 6 cm under arcus costa while the treatment was started. He had benefit from Ruxolitinib, thus spleen size in physical examination decreased to 4 cm under costa and clinical sypmtoms improved. After 2 years treatment with Ruxolitinib, he applied to our clinic with the complaint of painful lesions that appeared suddenly. In physical examination, rash in left inguinal region with diameter of 10-15 cm was seen. After tests it was realized that he had varisella zoster infection. He was given valacylovir (Valtrex 3x2 tablets) treatment and Ruxolitinib treatment was discontinued. After two weeks, the rash and painful lesions disappeared so, the treatment was started again.

Discussion

Localized and/or systemic infections can occur in the patients treated with Ruxolitinib but they are generally mild. Most infections resolve after an adequate course of oral antimicrobial therapy suggesting that prophylactic antimicrobial agents may not be necessary or cost-effective in the vast majority of MPD patients treated with Ruxolitinib [11]. In our present patient cohort, there is certain association between VZV infections and Ruxolitinib therapy of MPD. Clinical trials of Ruxolitinib suggested first clues regarding the infection rate of Ruxolitinib therapy in MPD (increased frequency in the Ruxolitinib arms included urinary tract infection (7.3% vs. 4.6% on placebo and 2.7% on BAT), and herpes zoster (4.0% vs. 0.7% on placebo and 0% on BAT) [6-10,17-19]. Heine et al. suggested identifying patients receiving Ruxolitinib, who are at risk for developing infections in a way similar to how prophylaxis strategies are determined for patients receiving anti-cytokine or B-cell–depleting therapies in the field of Hematology [20].

Ruxolitinib was approved in the treatment of MF-related splenomegaly or symptoms. These approvals were based on the data from two randomized Phase III studies: COMFORT-I randomized against placebo, and COMFORT-II randomized against best available therapy. In these studies, Ruxolitinib rapidly improved multiple disease manifestations of MF, reducing splenomegaly and improving quality of life of patients and potentially prolonging survival [2]. Although Ruxolitinib therapy is associated with some adverse events, such as anemia and thrombocytopenia, the overall risk/ benefit ratio of Ruxolitinib is absolutely acceptable when compared to the aggressive clinical course of MPDs, particularly MF. Our findings indicating the association between VZV infections and Ruxolitinib therapy of MPD shall be an alert for the careful follow-up of those patients. The anti-viral treatment was successful in all cases, however the prophylaxis strategies as suggested by the Heine group [20] has never been tested in clinical trials.

The pharmacological of physiologic JAK-STAT signaling via Ruxolitinib, especially in the context of multi-JAK inhibition, affects the lymphocyte homeostasis [21]. Herpes can complicate hematologically immunocompromised patients [22]. The dendritic cell-lymphocyte effect is associated with the Ruxolitinib-induced downregulation of IL-6, IL-8, TNF-α, interferon-gamma, IL-1Ra, and other inflammatory cytokines. The cytokine modulation is beneficial for MF. However, the immunomodulation can also cause a tendency for the complicating infections [12,20]. Our case reports in this present manuscript add their voices to this ultimate conclusion.

The clinical spectrum of Ruxolitinib is expanding. Recent RESPONSE phase III trial compared Ruxolitinib with BAT in patients with PV who were intolerant of or resistant to HU [18]. The primary study endpoint (a composite of hematocrit control and ≥ 35% spleen volume reduction at Week 32) was achieved by 21% of patients in the Ruxolitinib arm vs. 1% in the BAT arm ($P<0.0001$); 77% of patients in the Ruxolitinib arm achieved at least one component of the primary endpoint. The frequency, seriousness and severity of infection AEs in Ruxolitinib-treated patients with PV were less when compared to those in patients with MF in the RESPONSE trial. Urinary tract infections, mostly of Grade 1-2 severity, were reported at a slightly higher frequency in Ruxolitinib-treated patients. Herpes zoster was reported only in Ruxolitinib-treated patients with PV but the majority of these events were of Grade 1 or 2, self-limited, and none led to the discontinuation of study drug. Infections (excluding herpes zoster and urinary tract infections) of any grade or Grade 3-4 were reported at a comparable frequency between Ruxolitinib and BAT treated patients with PV [18]. JAK-STAT neoplastic signaling system is associated with the development of numerous neoplastic hematological diseases [23]. Therefore, the already approved JAK1/JAK2 inhibitor drug, Ruxolitinib, will be registered for the management of many additional neoplastic/ immune diseases, as well as MPD based on the results of ongoing clinical trials. Physicians prescribing Ruxolitinib should be alert of the VZV infections in the patients and proper anti-viral treatment and/or prophylaxis shall be considered in due course.

Conflict of Interest

The authors declare that they have no conflict of interest.

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