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A Case Report of Invasive Aspergillosis in a Patient Treated with Ruxolitinib

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Abstract

Invasive Aspergillosis (IA) is a severe opportunistic infection that typically affects immunocompromised patients. Ruxolitinib is a selective Janus kinase inhibitor which is used for steroid-refractory acute Graft-*vs*.-Host Disease (GVHD). Several case reports have described serious opportunistic infections in Ruxolitinib-treated Primary Myelofibrosis (PMF) patients but no routine antifungal prophylaxis is recommended in these patients. We present an interesting case of 77-year-old man with previous history of treated MDS several years ago currently on Ruxolitinib for GVHD who was found to have new cavitary lung lesion on routine imaging.

Keywords: Invasive aspergillosis • Ruxolitinib • GVHD

Introduction

Ruxolitinib, an inhibitor of Janus-Associated Kinases (JAK) 1 and 2, was initially approved by the FDA in 2011 for the treatment of myelofibrosis and was later approved for polycythemia vera in 2014 [1]. In the initial randomized clinical trials, ruxolitinib treatment exerted hematological side effects, mainly dose-related anemia, thrombocytopenia and neutropenia, while data on infections were not initially systematically captured, with the exception of a signal for herpes zoster virus infections [2]. Given the prominent role of JAK/STAT signaling downstream of diverse cytokine receptors, increasing evidence suggests that ruxolitinib-dependent JAK1/2 inhibition exerts immunosuppressive effects, leading to enhanced susceptibility to infection [3]. In the case of fungal infections, the importance of JAK-STAT signaling downstream of type I-III interferons and other cytokines in host immune defense is beginning to unravel. For example, in neutrophils, cell-intrinsic STAT1 activation *via* IFN-λ/IFNLR1 signaling leads to reactive-oxygen species production for efficient Aspergillus clearance [4].

Herein, we present a patient who developed invasive aspergillosis while receiving ruxolitinib therapy for Graft *vs.* Host Disease (GVHD). This case report highlights the high degree of immunosuppression with ruxolitinib that may lead to invasive fungal infections in immunocompromised host and the need for heightened vigilance for opportunistic infections while on JAK 1 and 2 inhibitor medications like ruxolitinib.

Case Presentation

A 77-year-old male who presented to emergency department for dry cough and progressive exertional dyspnea since last few months. His medical history was notable for Myelodysplastic Syndrome (MDS) and he underwent Allogenic peripheral blood stem cell transplant from matched unrelated donor about 5 years ago. His post-transplant course was complicated with Graft *vs.* Host Disease (GVHD) manifesting as bronchiolitis obliterans 1 year after the transplant and he was treated with high dose steroids, tacrolimus and ruxolitinib. His steroids were successfully weaned off and he was only on Tacrolimus and ruxolitinib and was doing well.

On admission patient was afebrile, BP was stable, O_2 saturation was around 95% on 2 liters oxygen. Physical examination revealed awake and alert patient not in severe respiratory distress, chest auscultation revealed bilateral coarse crackles at bases. Cardiovascular exam showed no JVD, murmur or peripheral edema. Neuro exam was non-focal.

Initial laboratory studies revealed total white blood cell count 3.8, Absolute Neutrophil Count (ANC) was 2.4 and hemoglobin was 11, with platelet count of 164, serum creatinine was normal. LFTs were also unremarkable. Chest radiograph showed 4 cm Right Upper Lob (RUL) cavitary lesion (Figure 1). Computed tomography of chest was done which confirmed the RUL cavitary lesion. Blood cultures and sputum cultures were sent and patient was empirically started on broad spectrum antibiotics which were later discontinued after consultation with infectious disease. Further infectious work

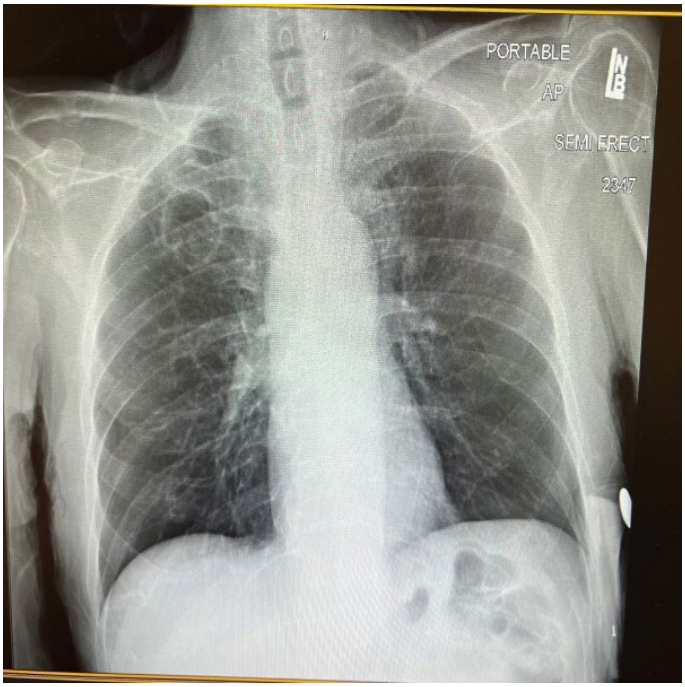

Figure 1. Chest radiograph AP view showing 4 cm right upper lobe cavitary lesion.

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up including fungal sputum cultures, sputum for AFB, serum beta D-glucan and galactomannan levels were also sent.

Pulmonology was consulted and patient was planned for bronchoscopy with bronchoalveolar lavage, but meanwhile sputum culture report came back with growth of mold. Patient was started on Voriconazole 6 mg/kg q12 hourly for 2 doses followed by 4 mg/kg q12h and ruxolitinib was held. Serum aspergillus Ag came back positive 1.52, serum beta-D glucan level was also significantly elevated to more than 500, cryptococcal antigen was negative. Patient ultimately underwent bronchoscopy with BAL which confirmed diagnosis of Aspergillus Fumigatus. Patient was continued on Voriconazole but unfortunately his respiratory status got worse and he was transferred to ICU and started on high flow oxygen followed by non-invasive ventilation with BiPAP. He also developed persistent visual hallucinations which were attributed to Voriconazole so it was switched to Isavuconazole. His respiratory status did deteriorate further, at this time CT chest was repeated and repeat cultures were sent to look for secondary causes of superimposed bacterial infections. CT chest showed worsening of cavitary lesions (Figure 2). His repeat blood cultures, sputum cultures and final BAL cultures were negative for bacterial infection and sputum for AFB smear was also negative for mycobacteria or non-tuberculous mycobacteria.

He was continued on Isavuconazole. Although his serum fungal markers level was trending down including beta D glucan and serum galactomannan levels but clinically patient got worse with encephalopathy and breathing did not improve so decision was made by the family to deescalate the care and not to proceed to endotracheal intubation. Patient was made DNR/DNI followed by Comfort Measures Only (CMO) and ultimately, he passed away.

Results and Discussion

Invasive Aspergillosis (IA) is a severe opportunistic infection that typically affects immunocompromised patients. Classic risk factors include chronic neutropenia, hematopoietic stem cell transplant and solid organ transplant, prolonged treatment with high corticoid doses, hematological tumors, cytotoxic chemotherapy, the acquired immunodeficiency syndrome and chronic granulomatous disease. Use of certain biologic agents such as Bruton's tyrosine kinase inhibitors and venetoclax, a B-cell leukemia/lymphoma-2 inhibitors also raise the risk of invasive aspergillosis. IA is characterized by progression of the infection across tissue planes. One hallmark of this infection is vascular invasion with subsequent infarction and tissue necrosis.

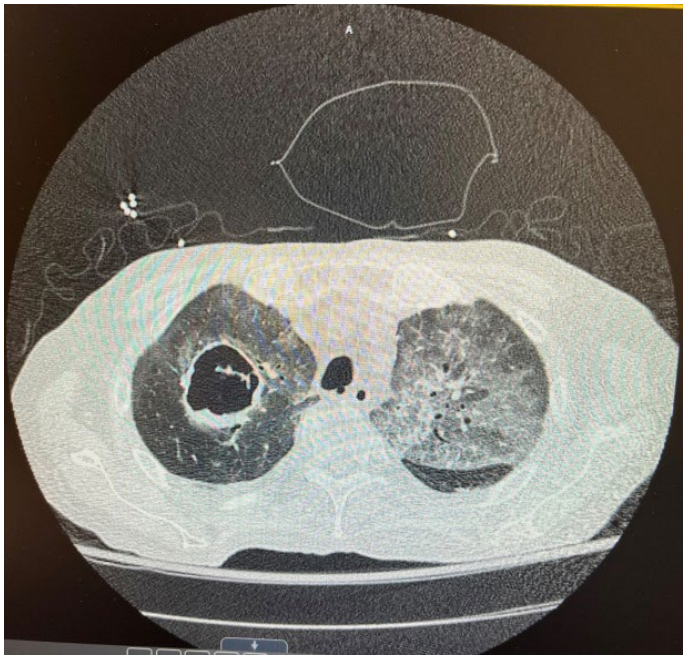

Figure 2. Computed tomography showing right upper lobe cavitary lesion with ground glass opacities more marked on right side.

Diagnosis of IA can be made by several different methods 3 such as histopathologic/cytologic and culture examination of tissue and fluid specimens, by serum and Bronchoalveolar Lavage (BAL) galactomannan assay by chest Computed Tomographic (CT) scan and by bronchoscopy with BAL.

Antifungal prophylaxis against Aspergillosis is recommended in patients with

- Hematologic disorders with poorly functioning neutrophils (e.g., aplastic anemia and variants thereof, MDS), acute leukemia with repeated and/or prolonged neutropenia, or a history of IA prior to transplantation.
- Chronic immunosuppression associated with GVHD (corticosteroid equivalent of >1 mg/kg/day of prednisone for >2 weeks and/or the use of other anti-GVHD therapies, such as lymphocyte-depleting agents, or Tumor Necrosis Factor α (TNF-α) inhibition, for refractory GVHD.
- Mold colonization pre- or post–lung transplant, mold infections found in explanted lungs, fungal infections of the sinus and single-lung transplant recipients, recipients receiving immunosuppression augmentation with either thymoglobulin, alemtuzumab, or high-dose corticosteroids.
- Other Solid Organ Transplant (SOT) recipients based on the institutional epidemiology of infection and assessment of individual risk factors [5].

Ruxolitinib is a selective Janus kinase inhibitor which was approved by Food and Drug Administration in May 2019, for steroid-refractory acute GVHD in adult and pediatric patients 12 years and older. It is also used for intermediate or high-risk myelofibrosis, including PMF, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis in adults.

Several case reports have described serious opportunistic infections in Ruxolitinib-treated PMF patients. A thorough literature review was done by Palma Manduzio to analyze the relationship among Ruxolitinib, immune system and infections [6]. Infections were recognized early and late after treatment. For bacterial infections; the majority of case reports described disseminated tuberculosis, including Pott's disease. For viral infections; it was Herpes Simplex Virus (HSV) possible reactivation and Hepatitis B Virus (HBV) reactivation and for fungal and protozoan infections; it was Pneumocystis Jiroveci (PJP), Cryptococcus and toxoplasma.

In another case report, a 30-year-old male with acute myeloblastic leukemia with complete remission and secondary myelodysplastic syndrome developed a graft-*vs*.-host disease treated with Ruxolitinib. The patient developed IA manifesting as retinal necrosis.

Conclusion

Although our patient was also on Tacrolimus and Ruxolitinib for chronic GVHD along with physiologic dosage of steroids for adrenal insufficiency, routine antifungal prophylaxis is not recommended in these patients. More data is needed to fully understand the effects of these immunosuppressive agents and whether or not antifungal prophylaxis should be provided in these patients. Precautions should be implemented to improve adequate screening, prophylaxis and prompt treatment of infections. Furthermore, the patients should be warned about the possibility of reactivation of infections.

References

1. Raedler, Lisa A. "Jakafi (Ruxolitinib): First FDA-approved medication for the treatment of patients with polycythemia vera." *Am Health Drug Benefits* 8 (2015): 75.
2. Vannucchi, Alessandro M., Jean Jacques Kiladjian, Martin Griesshammer and Tamas Masszi, et al. "Ruxolitinib *vs.* standard therapy for the treatment of polycythemia vera." *N Engl J Med* 372 (2015): 426-435.
3. McLornan, Donal P., Alesia A. Khan and Claire N. Harrison. "Immunological

consequences of JAK inhibition: Friend or foe?." *Curr Hematol Malig Rep* 10 (2015): 370-379.

4. Espinosa, Vanessa, Orchi Dutta, Constance Mc Elrath and Peicheng Du, et al. "Type III interferon is a critical regulator of innate antifungal immunity." *Sci Immunol* 2 (2017): 5357.
5. Walsh, Thomas J., Elias J. Anaissie, David W. Denning and Raoul Herbrecht, et al. "Treatment of aspergillosis: Clinical practice guidelines of the Infectious Diseases Society of America." *Clin Infect Dis* 46 (2008): 327-360.
6. Manduzio, Palma. "Ruxolitinib in myelofibrosis: To be or not to be an immune disruptor." *Ther Clin Risk Manag* (2017): 169-177.

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