Effect of Ruxolitinb in refractory pruritus in a patient with high-risk polycythemia vera A Case Report

Mohanned Karrar[1] and mohamed yassin[2]

[1]Hamad Medical Corporation
[2]HMC NCCCR

December 26, 2022

Abstract

Polycythemia vera (PV) associated pruritus is recognized as the most excruciating aspect of the disease. However, knowledge of pathophysiology, frequency, and precise character of PV-associated pruritus is limited. Ruxolitinib presented an encouraging and promising outcome in managing PV-related pruritus, especially in patients with symptoms refractory to other treatment modalities.

Introduction: -

Polycythemia vera is a Philadelphia-negative myeloproliferative neoplasm (MPN) characterized by increased red blood cell mass, bone marrow panmyelosis, and the presence of either a JAK2V617F or a JAK2 exon 12 mutations.

PV is diagnosed according to The World Health Organization by the presence of major diagnostic criteria, including an elevated hemoglobin or hematocrit level, abnormal results on bone marrow biopsy, and presence of the Janus kinase 2 genetic mutation, which is present in approximately 98% of cases. The only minor criterion is a subnormal erythropoietin level, which helps differentiate polycythemia vera from common causes of secondary erythrocytosis [1,2].

Patients with PV may experience a broad symptom burden that include constitutional symptoms such as fatigue, weight loss, night sweats and pruritus, mild-to moderate degree of splenomegaly, symptoms of hyperviscosity, microvascular symptoms (e.g., headaches, lightheadedness, visual disturbances, atypical chest pain, erythromelalgia, paresthesia), and thrombotic and bleeding complications [3,4].

Pruritus is one of the common clinical features of PV. In addition, PV-associated pruritus is often triggered by contact with water at any temperature, called 'aquagenic pruritus' (AP). Pruritus has been noted in 5–69% of PV patients.

PV-associated pruritus can directly result in substantially impaired quality of life. There are different ways to manage PV-related pruritis, including antihistamine, IFN-a 2b, Phototherapy, and cytoreduction.

Ruxolitinib, a JAK-2 inhibitor, recently started to be used to treat PV pruritis, especially in patients who had an inadequate response or had a side effect of hydroxyurea [1,5].

In this case, our PV patient had severe pruritis, which was not improving with antihistamine, local steroids, cytoreduction, and phlebotomy.

When we started the patient on low dose Ruxolitinib, the patient's symptoms improved slightly, so we increased the dose to a high dose which showed dramatic improvement.

Case Presentation: -

A 65-year Arabic female was diagnosed with PV in 2010 and followed in our outpatient clinic. She is also known to have dyslipidemia, Atrial fibrillation, and hypertension. She did not have a history of thromboembolic events. So, according to her age (>60 years) and presence of multiple comorbidities, she was categorized as having high-risk PV. She was started on peginterferon alpha 135 mcg every 12 weeks and phlebotomy as needed to keep her hematocrit below 42%. Her hematological indices were controlled.

In 2019, she presented to the primary health center complaining of generalized body itching. She was started on antihistamine and steroids ointments for a long time, but unfortunately, her itching did not improve.

In 2022, she started on a low dose of ruxolitinib (5 mg daily) based on the emerging evidence regarding its efficacy in PV cases with refractory symptoms. As a result, she started to improve regarding her itching but did not resolve it completely. So, after three months, the dose of ruxolitinib was increased to 10 mg, and she started to experience dramatically improved with complete resolution of itching.

She was followed for a few months and did not report any side effects with good tolerance of ruxolitinib.

Discussion: -

Pruritus is a common presentation in PV. It is characterized by the development of intense itching, stinging, tingling, or burning sensations without visible skin lesions.

It is commonly triggered by contact with water. However, its severity is variable and can be the most bothersome symptom in PV.

The underlying pathophysiology of PV-associated pruritus is poorly understood.

Most patients with PV patient found to have significantly increased mast cells in their skin. Also, it was found that in patients with Philadelphia-negative MPN, mast cells released greater levels of pruritogenic factors like histamine, leukotrienes, and interleukin-31. It was also found that in a patient with JAK2V617F mutation, basophil count was increased, and this mutation is also known to induce cytokine hypersensitivity in cell lines [3,5].

One theory mentioned that PV pruritus is due to the probable involvement of platelets (PLT) and prostaglandin. For example, platelet-rich plasma serotonin level is variably decreased in patients with PV, and PV-associated pruritus is sometimes controlled by treatment with selective serotonin reuptake inhibitors [6,7].

Treatment of PV-associated pruritus is a constant challenge.

The most frequently prescribed drugs are antihistamines; however, their effectiveness in reducing pruritus is variable. Other PV-associated pruritus treatment options include cytoreduction, phototherapy, interferon-alpha, SSRIs (e.g., paroxetine), pregabalin, and naltrexone. All were tried with different results [3,6].

As the target of HCT in the management of PV is less than 45%, reducing hematological parameters often improves PV symptoms, including pruritus. Phlebotomy showed mixed results. Also, hydroxyurea causes cytoreduction and can improve pruritus in some patients; it was found that 25% of the patient couldn't tolerate hydroxyurea. Interferon alfa (IFN-a) was found to be effective against PV-associated pruritus in some patients, but in the long term, it was found to have side effects that led to discontinuation of IFN-a in about 15% of patient [5,8].

Our patient was on INF-a for a long time. Her hematological indices were within the normal range, but pruritus was not controlled.

Ruxolitinib was approved for treating patients with PV who have an inadequate response to or are intolerant of hydroxyurea. Ruxolitinib is a JAK1/JAK2 inhibitor that leads to suppression of JAK-STAT signaling and reduction of cytokines and plasma levels of inflammatory markers, and this explains the improvement in PV-associated symptoms, including pruritus [9]. In 2017 the RELIEF study concluded that ruxolitinib

showed beneficial results in controlling PV-associated itchiness [10]. The RESPONSE-2 study showed that ruxolitinib has good hematocrit control, and improvement in disease-related symptoms, including pruritus, in comparison to hydroxyurea [11].

In our case, the use of ruxolitinib showed significant improvement in pruritus with complete resolution of the symptom.

Furthermore, our patient tolerated ruxolitinib treatment and reported no side effects over several months of follow-up.

Addressing the quality of life and trying to improve it [12,13],as well as answering the unanswered questions and unmet needs in MPNs are patient and hematologist necessity [14,15,16].

Conclusion: -

Pruritus is a common symptom in patients with PV resulting in significant morbidity. Amongst the many medications available for symptom control, ruxolitinib seems to be the most effective in managing PV-related pruritus. So, this case report sheds light on using ruxolitinib as the first-line treatment of refractory pruritus in PV patients.

Acknowledgments:-

We would like to acknowledge the Qatar Foundation for open access publication funding of this article.

Statement of Ethics:

The case was approved by Hamad Medical Corporation Research Center with reference number MRC-04-22-390.

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement:

The authors have no conflicts of interest to disclose.

Funding Sources:

Open access funding of this article was provided by Qatar Foundation.

Author contributions :

Conceptualization: Mohanned Abdalrahman Abdalwahed Karrar, Mohamed A Yassin.

Data curation: Mohanned Abdalrahman Abdalwahed Karrar, Mohamed A Yassin.

Writing – original draft : Mohanned Abdalrahman Abdalwahed Karrar, Mohamed A Yassin.

Writing – review & editing : Mohanned Abdalrahman Abdalwahed Karrar, Mohamed A Yassin.

Data Availability Statement:

All data generated or analyzed during this study are included in this published article. Further enquiries can be directed to the corresponding author.

References: -

1. Yassin MA, Taher A, Mathews V, Hou HA, Shamsi T, Tuğlular TF, et al. MERGE: A Multinational, Multicenter Observational Registry for Myeloproliferative Neoplasms in Asia, including Middle East, Turkey, and Algeria. Cancer Med. 2020 Jul;9(13):4512–26.

2. Barbui T, Thiele J, Gisslinger H, Kvasnicka HM, Vannucchi AM, Guglielmelli P, et al. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. Blood Cancer J. 2018 Feb 9;8(2):15.

3. Al-Mashdali AF, Kashgary WR, Yassin MA. Ruxolitinib (a JAK2 inhibitor) as an emerging therapy for refractory pruritis in a patient with low-risk polycythemia vera: A case report. Medicine (Baltimore). 2021 Nov 5;100(44):e27722.

4. Tefferi A, Vannucchi AM, Barbui T. Polycythemia vera treatment algorithm 2018. Blood Cancer J. 2018 Jan 10;8(1):3.

5. Saini KS, Patnaik MM, Tefferi A. Polycythemia vera-associated pruritus and its management. Eur J Clin Invest. 2010 Sep;40(9):828–34.

6. Lelonek E, Matusiak Ł, Wróbel T, Szepietowski JC. Aquagenic Pruritus in Polycythemia Vera: Clinical Characteristics. Acta Derm Venereol. 2018 Apr 27;98(5):496–500.

7. Gangat N, Strand JJ, Lasho TL, Li CY, Pardanani A, Tefferi A. Pruritus in polycythemia vera is associated with a lower risk of arterial thrombosis. Am J Hematol. 2008 Jun;83(6):451–3.

8. Silver RT. Long-term effects of the treatment of polycythemia vera with recombinant interferon-alpha. Cancer. 2006 Aug 1;107(3):451–8.

9. Verstovsek S, Passamonti F, Rambaldi A, Barosi G, Rosen PJ, Rumi E, et al. A phase 2 study of ruxolitinib, an oral JAK1 and JAK2 Inhibitor, in patients with advanced polycythemia vera who are refractory or intolerant to hydroxyurea. Cancer. 2014 Feb 15;120(4):513–20.

10. Mesa R, Vannucchi AM, Yacoub A, Zachee P, Garg M, Lyons R, et al. The efficacy and safety of continued hydroxycarbamide therapy versus switching to ruxolitinib in patients with polycythaemia vera: a randomized, double-blind, double-dummy, symptom study (RELIEF). Br J Haematol. 2017 Jan;176(1):76–85.

11. Griesshammer M, Saydam G, Palandri F, Benevolo G, Egyed M, Callum J, et al. Ruxolitinib for the treatment of inadequately controlled polycythemia vera without splenomegaly: 80-week follow-up from the RESPONSE-2 trial. Ann Hematol. 2018 Sep;97(9):1591–600.

12. Yassin MA, Al-Dewik NI, ElAyoubi H, Cassinat B. Efficacy and safety of pegelated interferon alpha2a once monthly compared to once weekly dose in patients with essential thrombocythemia. Blood. 2013 Nov 15;122(21):4054.

13. Taher A, Yassin MA, Xiao Z, Hou HA, Tuglular T, Mathews V, Rippin G, Sadek I, Siddiqui A, Wong RS. Impact of myeloproliferative neoplasms (MPNs) on health-related quality of life (HRQOL) and medical resource utilization: results from the MERGE registry. Blood. 2018 Nov 29;132:4311.

14. Yassin MA, Nehmeh SA, Nashwan AJ, Kohla SA, Mohamed SF, Ismail OM, Al Sabbagh A, Ibrahim F, Soliman DS, Szabados L, Fayad H. A study of 18F-FLT positron emission tomography/computed tomography imaging in cases of prefibrotic/early primary myelofibrosis and essential thrombocythemia. Medicine. 2020 Nov 6;99(45).

15. Sasi S, Mohamed M, Chitrambika P, Yassin MA. Myasthenia Gravis and Myeloproliferative Neoplasms–Mere Association or Paraneoplastic Neurologic Syndrome: A Mini-Review. Acta Bio Medica: Atenei Parmensis. 2022;92(6).

16. Ali EA, Abu-Tineh M, Hailan Y, Al-maharmeh QA, Maat ZO, Babiker AM, Ali B, Ismail AS, Yassin MA. The Outcome of Fatherhood in Patients with Philadelphia Negative Myeloproliferative Neoplasms, a Single Institution Experience ". Blood. 2021 Nov 23;138:4625.

16. Ali EA, Abu-Tineh M, Hailan Y, Al-maharmeh QA, Maat ZO, Babiker AM, Ali B, Ismail AS, Yassin MA. The Outcome of Fatherhood in Patients with Philadelphia Negative Myeloproliferative Neoplasms, a Single Institution Experience ". Blood. 2021 Nov 23;138:4625.