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Case Report

A Case of Myeloproliferative Neoplasm with Eosinophilia Associated with PCM1-JAK2 Rearrangement

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Keywords
PCM1-JAK2 · Myeloproliferative neoplasm · Pegylated interferon · Lenalidomide · Ruxolitinib

Abstract
Introduction: The PCM1-JAK2 rearrangement is generated through the t(8; 9)(p22; p24) translocation event. The myeloid/lymphoid neoplasms with eosinophilia (MLN-eo) with PCM1-JAK2 rearrangement is the common types of MLN-eo with tyrosine kinase fusion genes (MLN-Eo-tk). MLN-Eo with PCM1-JAK2 rearrangement is a rare disease with a poor prognosis and no unified treatment guidelines. The response of disease to ruxolitinib may be transient and it may only serve as a temporary treatment prior to transplantation. ***Case Presentation:*** We report 1 patient diagnosed with MLN-Eo with PCM1-JAK2 rearrangement who exhibited resistance to ruxolitinib, subsequently received pegylated interferon (Peg-IFN) and lenalidomide. The Peg-IFN was discontinued due to adverse effects; the patient has been receiving lenalidomide monotherapy for a duration exceeding 2 years, achieving complete hematologic remission and molecular response, significant amelioration of symptoms, as well as regression of hepatosplenomegaly. ***Conclusion:*** A case of MLN-Eo with PCM1-JAK2 rearrangement underwent continuous oral lenalidomide monotherapy for over 2 years. The patient achieved complete hematologic remission and molecular response during the long-term follow-up; however, a complete molecular remission was not attained. The underlying mechanism of lenalidomide in these diseases necessitates further comprehensive investigation through fundamental research and clinical trials.

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Introduction

The occurrence of translocations and rearrangements involving JAK2 are infrequent. Nevertheless, these mutations exert a significant impact on multiple hematopoietic cell lineages and have been reported in various hematological malignancies. The PCM1-JAK2 rearrangement caused by t(8;9)(p22;p24) is the most prevalent among them [1–3]. The International Consensus Classification (ICC) and World Health Organization (WHO) revised the diagnosis and classification of eosinophilic disorders in 2016, incorporating updated data and an enhanced understanding of disease molecular genetics. MLN-eo and gene rearrangements have been reclassified as MLN-Eo-tk, where the PCM1-JAK2 rearrangement serves as a representative member [4]. Patients with PCM1-JAK2 rearrangement typically exhibit clinical manifestations consistent with chronic myeloid neoplasms (such as myeloproliferative neoplasms, MPN or myelodysplastic/myeloproliferative neoplasms, MDS/MPN), often accompanied by eosinophilia, organomegaly, and bone marrow fibrosis in 50–70% of cases [3, 5]. The etiology behind the higher prevalence of MLN-Eo with PCM1-JAK2 rearrangement in males compared to females remains elusive. Bone marrow histopathology in these patients reveals distinct "triple findings" characterized by cellular proliferation accompanied by eosinophil infiltration, abundant aggregation of immature erythroid precursors, and bone marrow fibrosis [6]. The presence of erythroid hyperplasia and significant abnormalities in red blood cell production may give rise to other manifestations, certain cases may even exhibit abnormalities in granulocytic lineage and megakaryocytic lineage hematopoiesis [6]. Similar characteristics can also be observed in extramedullary sites, including the presence of large aggregates of immature red cell precursors [7], indicating the involvement of MLN-Eo with PCM1-JAK2 rearrangement in extramedullary regions.

MLN-Eo with PCM1-JAK2 rearrangement is a rare disease with a poor prognosis and no unified treatment guidelines. Currently, allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative approach for this disease. Ruxolitinib, a JAK2 inhibitor, has been demonstrated efficacy in certain patients with PCM1-JAK2 rearrangement myeloid neoplasms; however, the response to ruxolitinib may be transient and it may only serve as a temporary treatment prior to transplantation [8, 9]. We present a case of a patient with MLN-Eo with PCM1-JAK2 rearrangement who exhibited disease progression following administration of ruxolitinib treatment, indicating therapeutic inefficacy. The ruxolitinib was discontinued and a combination therapy of Peg-IFN with lenalidomide was initiated for treatment. The Peg-IFN therapy was discontinued after approximately 6 months due to adverse drug reactions, and the lenalidomide monotherapy was continued. The patient achieved complete hematologic remission and molecular response during long-term follow-up.

Case Presentation

In December 2020, a 47-year-old man was referred to the hematology department, who presented with a chief complaint of "persistent tinnitus for 2 years," accompanied by fatigue and dizziness lasting for 2 months. The physical examination revealed a pale complexion, a noticeable paleness of the conjunctiva, as well as paleness observed in both the lips and nail beds. No superficial lymph nodes were palpable throughout the body. There was no tenderness upon palpation of the lower sternum. The abdomen appeared flat with no visible varicose veins on its wall. The liver span was measured 2.6 cm below the rib margin, while the spleen was measured 4.6 cm below the rib margin. The patient had no prior medical history of chronic conditions such as hypertension or diabetes, and there was no evidence of exposure to hazardous substances such as radiation or chemicals. There was no documented familial

history of hereditary disorders. The admission blood routine revealed leukocytosis (leukocyte 36.78 × 10^9/L) with eosinophilia (eosinophils 7.7 × 10^9/L), and anemia (hemoglobin 77 g/L), and thrombocytopenia (platelet 80 × 10^9/L). A bone marrow aspiration was performed and revealed marked active proliferation in the bone marrow smear characterized by an elevated proportion of eosinophils at approximately 9.5 percent. The peripheral smear demonstrated the presence of immature granulocytes and eosinophils accounting for about 14 percent, as well as notable findings of immature red blood cells and teardrop-shaped erythrocytes. The bone marrow biopsy revealed a significantly active hematopoietic tissue, comprising approximately eighty to eighty-five percent of the volume. There was a decreased proliferation of adipose tissue and an increased granulocyte proliferation with a higher ratio. Scattered presence of immature precursor cells, mainly in the intermediate stage or below, as well as eosinophilic granulocytes without apparent morphological abnormalities was observed. Additionally, there was reduced erythroid proliferation and a reduced number of megakaryocytes (0–3/HPF) with uneven distribution including some small-sized cells. Scattered lymphocytes and plasma cells or small clusters were distributed along with regional fibrous tissue hyperplasia (Fig. 1). The reticular staining showed a grade between zero to one [10]. The cell immunotyping analysis revealed a significantly reduced proportion of myeloid progenitor cells, exhibiting no apparent abnormal expression. Eosinophilic granulocytes constituted 15.29 percent of the total nucleated cell population. The *BCR/ABL* gene and MPN-related genes (*JAK2 V617*, *CALR*, *W515L*, *JAK2 exon12*) were negative*; BCR-JAK2*, *ETV6-JAK2*, *ETV6-FLT3*, *ETV6-ABL1*, *PDGFRB*, *PDGFRA*, *FGRFR1* were also negative, only PCM1/JAK2 was positive. Chromosome analysis revealed a normal karyotype. The patient was diagnosed with MLN-Eo accompanied by PCM1-JAK2 rearrangement. Ruxolitinib treatment was initiated, and the dosage was adjusted based on platelet count, ranging from 5 mg to 15 mg per dose, twice daily. During the treatment period, the patient's follow-up blood routine at the local hospital exhibited fluctuations in white blood cell count ranging from 1.66 to 69.2 × 10^9/L, hemoglobin levels ranging from 51 to 109 g/L, and platelet count ranging from 18 to 67 × 10^9/L. Intermittent administration of oral hydroxyurea tablets and transfusion support were provided. The patient has been undergoing ruxolitinib treatment for approximately 4 months.

In May 2021, the patient presented to our department with complaints of persistent dizziness, tinnitus, fatigue, and numbness in all four limbs without significant improvement. The patient presented with a nonproductive dry cough and bilateral lower extremity edema. Upon admission, a physical examination revealed anemic appearance and ecchymosis. The liver edge was non-palpable below the costal margin, while the spleen measured 8 cm below the rib margin. Admission blood routine indicated white blood cells (51.05 × 10^9/L) and eosinophils (6.85 × 10^9/L), a decrease in hemoglobin level (70 g/L), and a low platelet count (36 × 10^9/L), indicating that the disease is worsening. The abdominal CT scan was performed with contrast enhancement to demonstrate splenomegaly, as well as compression and displacement of the left kidney, along with splenic infarction. Repeated bone marrow puncture examinations demonstrated active hematopoiesis characterized by an elevated granulocyte ratio and 2 percent eosinophils. Peripheral blood count showed 7 nucleated red blood cells out of 100 red blood cells. The bone marrow biopsy results revealed an increased proliferation of granulocytes, with scattered immature precursor cells at intermediate and early stages being the predominant cell types. Additionally, there was an elevated proportion of morphologically normal eosinophilic granulocytes. Erythropoiesis exhibited a decrease, however, visible distribution of erythrocyte precursors could be observed in certain areas. Megakaryocyte proliferation (0–4/HPF) with scattered normal-sized morphologies throughout the tissue was present. Lymphocytes and plasma cells were dispersedly distributed. Fibrous tissue hyperplasia, the reticular staining showed a grade between two and three. The result of the PCM1-JAK2 rearrangement was positive with a copy number of 217.3

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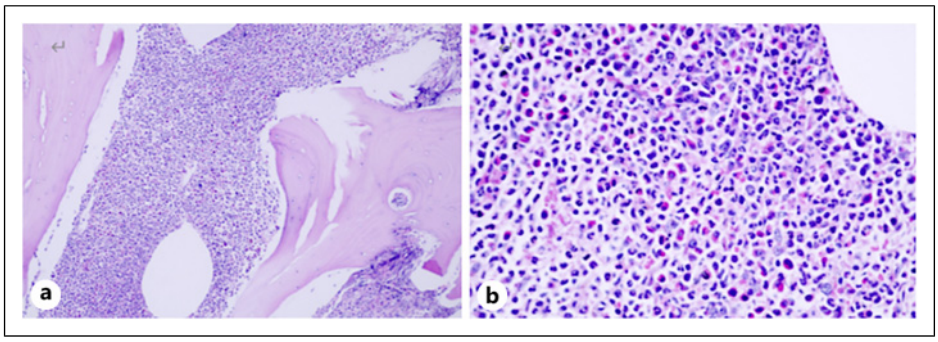

Fig. 1. a Optical magnification is 10×10. **b** Optical magnification is 10×40. Hematoxylin and eosin (HE) staining showing cellular proliferation accompanied by eosinophil infiltration and bone marrow fibrosis. The typical "triple findings" were not observed in this case.

percent. The patient received blood transfusion and anticoagulation therapy. However, due to the intolerable disease progression observed during ruxolitinib treatment, it was discontinued and replaced with Peg-IFN (180 μg ih QW).

One month later, the patient's white blood cells (10.24×10^9/L) and eosinophils (2.60×10^9/L) decreased significantly, anemia was improved, but the platelet (17×10^9/L) was decreased. Due to a significantly low platelet count, necessitating hospitalization for repeated platelet transfusions, subsequent abdominal CT scans revealed consistent findings of splenomegaly and infarction as previously observed. Consequently, a daily oral dose of 10 mg lenalidomide was administered for treatment. Subsequent follow-up blood tests revealed a gradual recovery and stabilization of leukocyte, erythrocyte, and thrombocyte counts (Fig. 2), accompanied by improved hepatosplenomegaly. However, following 6 months of Peg-IFN therapy, the patient developed ischemic optic neuropathy in his left eye as an adverse effect associated with Peg-IFN administration. As a result, Peg-IFN treatment was terminated. allo-HSCT was suggested as a potential bridging therapy, nevertheless, financial limitations hindered its feasibility for the patient. Subsequently, monotherapy with oral lenalidomide was continued while closely monitoring alterations in blood routine indicators throughout this duration. Surprisingly, after nearly 2 years of monotherapy with oral lenalidomide, regular follow-up blood tests conducted at the local hospital showed normal results, along with complete hematological remission achieved and good overall physical condition maintained. However, due to suboptimal patient adherence, regular updates on bone marrow aspiration cytology examination or *PCM1-JAK2* gene quantification assessment for molecular response evaluation were not available. Despite our recent repeated recommendations regarding PCM1-JAK2 rearrangement resulting in a copy number of 0.43 percent, indicating achieved molecular response; the bone marrow biopsy revealed reticulin staining was grade of one.

Discussion

Previous studies have demonstrated the inhibitory effects of ruxolitinib on PCM1-JAK2 transformed Ba/F3 mouse cells in vitro, as well as its ability to suppress phosphorylation of the JAK-STAT5 signaling pathway [8]. Ruxolitinib, a potent JAK2 inhibitor commonly used for the treatment of polycythemia vera and myelofibrosis [11], has been assessed in various cell lines harboring distinct JAK2 fusion mutations, including PCM1-JAK2. Prominent clinical responses, such as achieving hematologic remission, have been observed in patients with this specific subtype of MPN who underwent treatment with ruxolitinib [9]; however, these effects may be

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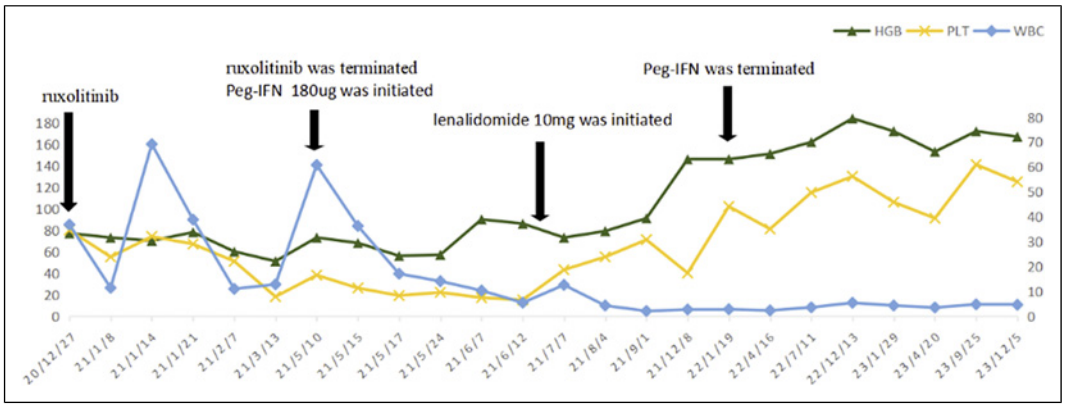

Fig. 2. Blood cell changes in patient over the course of the disease.

transient. Yingxin Sun et al. [12] reported a case of a male patient diagnosed with MLN-Eo accompanied by PCM1-JAK2 rearrangement. Initially, the patient achieved rapid hematologic remission following treatment with ruxolitinib and hydroxyurea, however, subsequently experienced progressive leukocytosis and eosinophilia, indicating therapeutic failure. After the administration of Peg-IFN, a significant reduction in the copy number of the PCM1-JAK2 rearrangement was observed, indicating a molecular response. However, due to limited follow-up duration, complete achievement of molecular remission was not observed in this patient. Consequently, the patient is currently undergoing preparations for allo-HSCT as a bridging therapy.

We present a case report of a male patient diagnosed with MLN-Eo accompanied by PCM1-JAK2 rearrangement. Despite receiving oral ruxolitinib treatment for over 4 months, the disease continued to progress, indicating a failure in treatment. The patient presented with clinical bleeding and subsequently developed new-onset splenic infarction, which led to the discontinuation of ruxolitinib. Peg-IFN was administered as an alternative treatment for 1 month, followed by the addition of lenalidomide as adjunctive therapy. After 6 months of using Peg-IFN, monotherapy with lenalidomide was initiated orally. The patient's liver and spleen have exhibited a significant reduction in size, accompanied by notable improvements in clinical symptoms and quality of life. Moreover, complete hematological remission has been achieved, along with the attainment of molecular response. Importantly, the incorporation of lenalidomide into the treatment regimen resulted in a sustained recovery of hemoglobin levels until they reached normalization and stability. The white blood cell count consistently decreased until it reached normal levels and remained stable. Additionally, the platelet count exhibited significant recovery despite a transient decrease during treatment but rapidly returned to within the normal range (Fig. 2). The patient has been receiving lenalidomide monotherapy for over 2 years, demonstrating consistently normal counts across all three hematological series in routine blood examinations, while exhibiting remarkable improvement in the degree of bone marrow fibrosis as well as a notable reduction in the copy number of PCM1-JAK2 rearrangement. We postulate that lenalidomide has played a pivotal therapeutic role throughout the management process of this patient's disease.

This report presents the inaugural utilization of lenalidomide in patients with MLN-Eo with PCM1-JAK2 rearrangement. Previous studies have demonstrated the immunomodulatory properties of lenalidomide, which can partially ameliorate anemia and thrombocytopenia in individuals with bone marrow fibrosis while also exerting a spleen-reducing effect. Emerging evidence suggests that both thalidomide and lenalidomide provide significant clinical benefits for patients with myelofibrosis, primarily through the alleviation of anemia and extension of survival, however, in comparison to thalidomide, lenalidomide is linked to a lower incidence of adverse effects [13]. Research indicates that pomalidomide exhibits a

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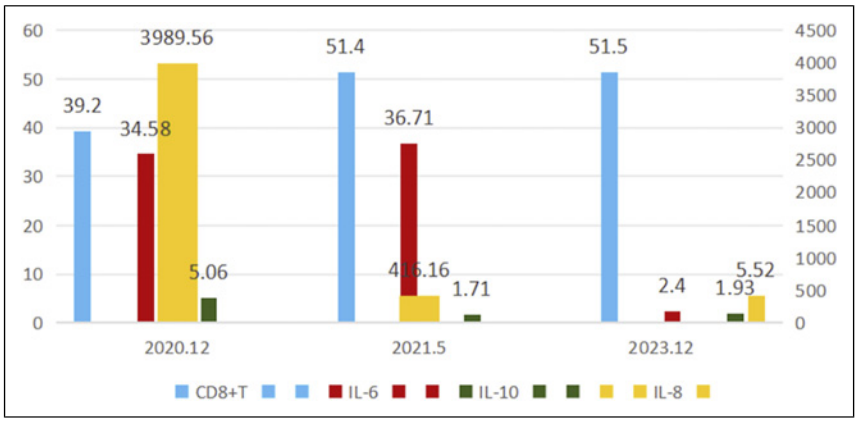

Fig. 3. Changes in patient cytokines and CD8+T cells before and after treatment.

notable efficacy in primary myelofibrosis, significantly alleviating anemia and thrombocytopenia in affected patients. However, due to the high cost associated with pomalidomide, we opted for treatment with lenalidomide [14]. According to pertinent literature, the recommended dosage of lenalidomide for myelofibrosis is 10 mg [15]. Consequently, the patient we reported received treatment with 10 mg of lenalidomide.

The decision to employ lenalidomide was based on two factors: first, lenalidomide exhibits broad anti-inflammatory, antiangiogenic, antiproliferative, and immune-regulating effects by inhibiting NF-κB-mediated pro-inflammatory and apoptotic cytokines such as IL receptor 2 (IL-2R), interleukin 6 (IL-6), interleukin 10 (IL-10), interleukin 8 (IL-8), interleukin 15 (IL-15),transforming growth factor beta (TGF-β), basic fibroblast growth factor (bFGF), tumor necrosis factor alpha (TNF-alpha), and vascular endothelial growth factor (VEGF). Simultaneously, it upregulates the expression of interleukin 2 (IL-2) and interferon gamma (INF-γ). Additionally, it directly activates cytotoxic/regulatory T cells and enhances natural killer (NK) cell activity [16]. Second, lenalidomide enhances the ubiquitination and subsequent degradation of specific substrates mediated by E3 ubiquitin ligases, leading to rapid and selective degradation of Aiolos (IKZF3) in lymphocytes [17]. Aiolos belongs to the Ikaros zinc finger protein (IKZF) family, which not only plays a pivotal role in determining and maturing the eosinophil lineage but also exerts significant influence on eosinophil functional responses. It regulates cell migration and cancer metastasis by disrupting intercellular and epithelial interactions while attenuating chemokine receptor and integrin function [17].

Therefore, lenalidomide has the potential to impede the development, maturation, and functional response of eosinophils. Patients with MLN-Eo with PCM1-JAK2 rearrangement typically exhibit significantly elevated levels of eosinophils; however, there is currently no available literature on immune dysregulation in such patients. Further basic and clinical trials are imperative to assess immune dysregulation in this specific patient population. In this case report, we observed higher levels of IL-6, IL-8, and IL-10 cytokines in the patient's serum prior to treatment. Subsequent reassessment after lenalidomide treatment demonstrated normalization of these cytokine levels. Moreover, flow cytometry analysis revealed an augmentation in cytotoxic T lymphocyte levels following lenalidomide treatment (Fig. 3), which is consistent with existing literature on the immunoregulatory effects of lenalidomide. However, due to inadequate compliance reasons for this patient's failure to undergo testing for cytokine and lymphocyte levels before and after Peg-IFN therapy were not ascertained solely based on this single case study. Therefore, further research encompassing both fundamental scientific investigations and clinical studies is warranted.

Conclusion

The occurrence of MPN-Eo with PCM1-JAK2 rearrangement is infrequent and associated with an unfavorable prognosis. Ruxolitinib often exhibits transient efficacy and may even be ineffective in certain patients. In our report, lenalidomide was first attempt to achieve a complete hematological and molecular response, as well as a significant improvement in the overall quality of life. A promising treatment of lenalidomide for MPN-Eo with PCM1-JAK2 rearrangement. Lenalidomide was initially investigated in this disease due to its therapeutic mechanism, which necessitates further comprehensive investigation through both fundamental and clinical research.

Statement of Ethics

This study protocol was reviewed and the need for approval was waived by Lanzhou University Second Hospital Ethics Committee. 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 declare.

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Author Contributions

Writing: Wen Zhou; conceptualization and review and editing: Liansheng Zhang and Lijuan Li; investigation: Xiaojia Guo and Zhengdong Hao; formal analysis: Yang Liu; data curation: Songlin Chu; supervision: Liansheng Zhang and Lijuan Li. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (available at https://doi.org/10.1159/000542692).

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