

Mantle Cell Lymphoma in a Patient with Polycythemia Vera: Coincidence or Causal Link?

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Abstract

Case Report

Myeloproliferative neoplasms (MPNs) are chronic hematologic disorders marked by the clonal proliferation of myeloid precursors, leading to the overproduction of mature blood cells. Although the concurrent occurrence of myeloproliferative and lymphoid neoplasms is rare, epidemiological studies indicate an increased risk of secondary non-myeloid malignancies, particularly lymphoproliferative syndromes, in patients with MPNs. We present a case of a 52-year-old woman diagnosed with polycythemia vera treated with hydroxycarbamide, who subsequently developed mantle cell lymphoma (MCL), a subtype of B-cell non-Hodgkin lymphoma, after five years. The patient underwent two cycles of R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone). Unfortunately, the patient died due to infectious complications. The coexistence of MPNs and lymphoid neoplasms is rare but clinically significant. The elevated risk of lymphoid neoplasms in patients with MPNs may be due to chronic inflammation, JAK2 mutations, genetic predispositions, and cytoreductive therapies. This case underscores the importance of vigilant monitoring for secondary malignancies in MPN patients and highlights the complex interplay between genetic and environmental factors in disease progression. This case report contributes to the growing body of evidence linking chronic inflammation and JAK2 mutations with secondary lymphoid neoplasms in MPN patients. Further research is essential to understand the underlying mechanisms of this association and to develop effective prevention and treatment strategies.

Keywords: Myeloproliferative Neoplasms, Polycythemia Vera, Mantle Cell Lymphoma, JAK2 V617F Mutation, JAK inhibitors.

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INTRODUCTION

Myeloproliferative neoplasms (MPNs) are chronic hematologic diseases affecting the myeloid lineage. They are due to an acquired clonal abnormality of the hematopoietic stem cell that results in the proliferation of myeloid precursors of one or more lineages with complete differentiation and maturation of cells [1]. They are classified according to the 2016 WHO classification based on the detection of genetic alterations such as the BCR-ABL fusion gene, which results from a reciprocal translocation between chromosomes 9 and 22 t(9;22) (q34;q11), leading to the Philadelphia chromosome (Ph), and includes chronic myeloid leukemia. Ph-negative myeloid neoplasms include Polycythemia Vera (PV), Essential Thrombocythemia (ET), Primary Myelofibrosis (PMF), and other rarer MPNs: chronic neutrophilic leukemia, chronic eosinophilic leukemia, mastocytoses, and unclassifiable MPNs [1].

Numerous epidemiological studies have demonstrated an increased risk of developing a second non-myeloid cancer, particularly a lymphoproliferative syndrome, in patients with MPNs [2, 3]. It is suggested that chronic inflammation [4], activation of the JAK2 signaling pathway [5], genetic background [6–9], and treatment with Janus kinase inhibitors [10, 11], could play a role in the development of lymphoma in patients with myeloproliferative neoplasms. We present a case report of an atypical form of mantle cell lymphoma (MCL), a subtype of B-cell non-Hodgkin lymphoma, in a patient with polycythemia vera under hydroxycarbamide treatment.

CASE REPORT

A 52-year-old woman, with no significant medical history, consulted in 2018 for asthenia and signs of hyperviscosity such as headaches, dizziness, and facial erythema. Clinical examination revealed massive splenomegaly reaching the umbilicus. Blood tests

showed hemoglobin at 16.1 g/dl, hematocrit at 50%, white blood cells at 20 G/L, neutrophils at 16 G/L, lymphocytes at 2.4 G/L, and platelets at 473 G/L, with a normal blood smear. FISH testing confirmed the presence of the V617F mutation in the JAK-2 gene.

Histopathological examination of the bone biopsy confirmed the diagnosis of polycythemia vera. An abdominal ultrasound showed homogeneous splenomegaly measuring 190x120 mm. The diagnosis of polycythemia vera was confirmed with the presence of three major criteria: Hb > 16 g/dl, the presence of the V617F mutation, and histological criteria.

Treatment with hydroxycarbamide and acetylsalicylic acid was initiated. The evolution was marked by significant improvement in general symptoms, with hemoglobin decreasing to 13.4 g/dl and hematocrit to 43% after three months of treatment. Hydroxycarbamide was maintained.

In January 2023, the patient presented with progressively worsening dyspnea, asthenia, pallor, and abdominal pain. Clinical findings included bilateral 2 cm cervical lymphadenopathy, right pleural effusion, abdominal distension with splenomegaly extending beyond the umbilicus, and hepatomegaly. Blood tests revealed hemoglobin concentration at 7.6 g/dl, hematocrit at 30%, white blood cells at 46 G/L, neutrophils at 11 G/L, lymphocytes at 37 G/L, and platelets at 240 G/L. The blood smear showed medium-sized lymphocytes with large, regular-contoured nuclei, sometimes notched, with decondensed chromatin and scant basophilic cytoplasm. Ten percent of prolymphocytes and numerous Gumprecht shadows were also noted. Lymphocyte immunophenotyping confirmed the circulating phase of a CD5+ B-cell non-Hodgkin lymphoma, with a Matutes score of 1/5.

A thoraco-abdomino-pelvic CT scan revealed bilateral supraclavicular lymphadenopathy of 13 mm, moderate right pleural effusion, massive splenomegaly measuring 270x200 mm with multiple infarcted areas, hepatomegaly of 240 mm, and a dilated portal trunk of 20 mm.

Histopathological examination of the bone biopsy also showed marrow infiltration by mantle cell lymphoma, with strong expression of CD20 and CD5, positivity for cyclin D1, negativity for CD138, CD2, and MPO, and a low proliferation index Ki67. The clinical stage was determined to be stage IV according to the Ann Arbor classification, with an international mantle cell lymphoma prognostic index of 5. The pleural biopsy suggested secondary pleural involvement of mantle cell lymphoma.

First-line chemotherapy of RDHAOX type was initiated on 18/08/2023. After the second cycle, the patient died due to infectious complications.

DISCUSSION

The coexistence of myeloproliferative neoplasms (MPNs) and lymphoid neoplasms is rare. However, the risk of lymphoid neoplasms is increased by 2.5 to 3.5 times in patients with chronic myeloproliferative neoplasms compared to the general population [2, 3]. This situation could result from various factors, including the consequences of chronic inflammation [4], the combination of acquired mutations in the Janus kinase 2 (JAK2) gene [5], genetic predisposition [6–9], and the influence of cytoreductive treatments [10, 11].

Ph-negative myeloproliferative neoplasms, particularly myelofibrosis, are considered an inflammatory disease model, where chronic inflammation can play a crucial role in disease progression and the development of secondary neoplasms [6]. Chronic inflammation induces increased cytokine production, oxidative stress with increased reactive oxygen species (ROS), contributing to epigenetic changes and DNA mutations favoring tumorigenesis [6]. Immune abnormalities, notably a significant increase in myeloid-derived suppressor cells (MDSCs), are observed in Ph-negative MPNs, interfering with immune surveillance [12].

The acquired somatic mutation in the Janus kinase 2 (JAK2) gene, particularly the V617F mutation, plays a crucial role in the development of classical myeloproliferative neoplasms (MPNs) [1]. It occurs in more than 95% of patients with PV and in 50% to 60% of patients with ET or PMF [13]. JAK2-mediated signaling promotes the phosphorylation of STAT3 and STAT5 transcription factors, contributing to the transcription of genes regulating cell proliferation, differentiation, and apoptosis [14]. JAK2 kinase also exerts oncogenic effects through epigenomic alterations [15]. In lymphomas, JAK2 mutations are rare. JAK/STAT pathway activation occurs via JAK2 amplification due to an increased number of copies of the 9p24 region [16]. The overexpression of wild-type JAK2 protein induces the transcription of the interleukin-13 (IL13) gene [17], and the transcription of PD-1, PD-L1, and PD-L2 ligands located on chromosome 9p24 [18]. The interaction between PD-1 and its ligand inhibits T cell function and increases regulatory T cell (Treg) function, weakening antitumor immunity [18].

Genetically, a germline haplotype (GGCC, designated "46/1") encompassing the 30 region of JAK2 is associated with a three to fourfold increased risk of developing V617F-positive MPNs. A germline sequence variant identified in TERT rs2736100_C, the second intron of TERT, which encodes the reverse transcriptase component of the telomerase complex, has been identified as a second predisposing factor for MPNs [6]. Additionally, other predisposing alleles in the MECOM, HBS1L-MYB, SH2B3, TET2, ATM, CHEK2, PINT,

and GFI1B genes have been identified in MPN patients [7, 8].

The potential role of JAK inhibitors in lymphomagenesis remains ambiguous. Besides the altered immune surveillance observed in myeloproliferative neoplasms [12], JAK inhibitor treatment may be associated with a reduction in NK cells [19], a quantitative and functional alteration of dendritic cells [20], a notable decrease in inflammatory cytokine secretion by CD4+ T cells, and a significant reduction in Tregs [21].

Recently, an Austrian study by Porpaczy suggested that JAK inhibitor treatment for myelofibrosis may be associated with an increased risk of aggressive B-cell lymphomas [10]. The lymphomas developed in the Austrian cohort were all negative for the JAK2V617F mutation compared to their counterpart and developed from a pre-existing B-cell clone detectable at early stages of MPN, showing extranodal involvement and high MYC and BCL2 expression [10]. Therefore, detecting a pre-existing B-cell clone could identify individuals at risk.

The hypothesis of the pre-existing B-cell clone's role in the occurrence of B-cell lymphoma after ruxolitinib treatment was reinforced by Elisa Rumi in an Italian cohort. This study showed a low rate of lymphoproliferative disorders in MPN patients (24/3069, 0.78%) but higher than expected in the general population. Additionally, it was not associated with prior ruxolitinib exposure. It should be noted that none of these patients presented B cell clonality in the peripheral blood before ruxolitinib treatment [11].

Furthermore, Pemmaraju *et al.*, found no significant difference in lymphoma incidence when comparing patients treated with JAK inhibitors to those who were not treated [22]. Moreover, a recent Italian study recorded no cases of lymphoma development, with a median follow-up duration after the start of ruxolitinib similar to that of the Porpaczy study [23].

CONCLUSION

Chronic inflammation, as the main driver of disease progression in MPNs, paves the way for clinical trials evaluating the efficacy of the combination of interferon- α and ruxolitinib in the early stages of MPNs. Recently, a phase II study demonstrated that the combination of ruxolitinib and low-dose PEGylated interferon- α 2 (PEG-IFN α 2) improved blood cell counts, reduced bone marrow fibrosis, and decreased the JAK2 V617F allele burden with acceptable toxicity in several patients with polycythemia vera or myelofibrosis [24].

Thus, the role of the JAK/STAT pathway in the pathophysiology of myeloid and lymphoid disorders has recently opened new therapeutic perspectives. Ruxolitinib has been tested in a phase II study in patients

with advanced, primarily refractory Hodgkin lymphoma, revealing promising results [25].

Long-term data on patients treated with JAK inhibitors are relatively limited compared to the well-established clinical experience with ruxolitinib.

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