






## Case Report

# Blastoid mantle cell lymphoma in a patient with chronic myeloproliferative neoplasia

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## Introduction

Myeloproliferative neoplasms (MPN) are a group of diseases characterized by clonal proliferation in chronic phase of the hematopoietic stem cell that originates one or more myeloid strains.<sup>1,2</sup> They are classified according to the detection of genetic alterations such as (I) the fusion gene BCR-ABL which results from a reciprocal translocation between chromosomes 9 and 22 t(9;22)(q34;q11), resulting in the Philadelphia (Ph) chromosome, and (II) Ph negative neoplasms including polycythemia vera, essential thrombocythemia and myelofibrosis, associated with JAK2 V617F (*Janus kinase 2*), CALR (*Calreticulin*) and MPL (*Trombopoietin receptor*) mutations, according to the WHO 2016 classification. The JAK2 mutation is considered integral to the myeloproliferative process, results in the loss of autoinhibitory control and incytokine-induced

hyperactivation of JAK2. Essential thrombocythemia and polycythemia vera might also progress to myelofibrosis and leukemia; secondary malignancies may occur with a low incidence. Patients with myeloproliferative neoplasms have higher risk of developing lymphoid neoplasm than the general population.<sup>1–6</sup>

Ruxolitinib is a selective inhibitor of JAK1 and JAK2, widely used for the treatment of high- and intermediate-risk DIPSS plus score prognosis of myelofibrosis, with the aim of improving splenomegaly and its associated symptoms.<sup>7</sup>

We present a case report of an atypical form of mantle cell lymphoma (MCL), a subtype of B-cell non-Hodgkin lymphoma, in patient with myeloproliferative neoplasms detected after the introduction of a JAK inhibitor, Ruxolitinib.

## Case report

A 85-year-old male, diagnosed with MPN not specified in 2008, characterized by thrombocytosis, presence of the JAK2 V617F mutation, BCR-ABL transcript negative, with no history of thrombosis. He had no bone marrow examination at diagnosis. He used hydroxyurea for a long period, approximately

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10 years, which was suspended in February/2019 due to the development of cytopenia and a 19cm splenomegaly. On this occasion, he also presented with B symptoms, acute deep vein thrombosis in the fibular vein and soleus bilaterally and his blood counts were as follows: hemoglobin 7,8g/dL, erythroblastosis, white blood cell (WBC)  $6.9 \times 10^9/L$  with absolute neutrophil count (ANC)  $3.7 \times 10^9/L$ , absolute lymphocyte count (ALC)  $2.2 \times 10^9/L$ , blasts 4%, platelets  $345 \times 10^9/L$ . Anti-coagulation with Rivaroxaban was started. He underwent bone marrow examination, which showed progression to myelofibrosis, without abnormal cells and a normal karyotype. His IPPS prognostic scores was high and DIPSS was intermediate plus 2. Hydroxyurea was reintroduced but, two months later, cytopenias developed again, leading to red blood cell transfusion dependence and worsening splenomegaly. Ruxolitinib was started 15 mg twice a day. At 2-weeks follow-up, there was a significant improvement in general symptoms, hemoglobin increase from 7 to 9,3 g/dL and a 2 cm reduction in the spleen size.

Concomitantly with clinical improvement, three weeks after Ruxolitinib introduction he developed a progressive increase WBC count of  $109 \times 10^9/L$  with ANC  $6 \times 10^9/L$ , ALC  $80 \times 10^9/L$  and absolute atypical cells  $19 \times 10^9/L$ . Evaluation of peripheral blood smear showed the presence of large cells, loose chromatin, evident nucleolus, without granules or Auer rods. Immunophenotyping by flow cytometry peripheral blood showed positivity for CD5, CD20 and CD19; CD23 was negative, consistent with a chronic lymphoproliferative disease. On physical examination, there was an enlargement of a cervical lymph node measuring 4 cm. Marrow biopsy was performed, confirming the diagnosis of blastoid mantle cell lymphoma by Immunohistochemistry (cyclin D1, CD20, CD5 and myeloperoxidase positive, Ki67 90%). Unfortunately, at this stage, the patient was on performance status ECOG 4 and died from an infection, before specific therapy was started and was studied the presence of the JAK2 mutation in lymphoma cells.

## Discussion

There is an increased incidence of tumors, solid or hematological, in patients with myeloproliferative neoplasms.<sup>1</sup> One of the main causes of death related to MPN is the progression to acute myeloid leukemia, which occurs in about 20% of patients.

The diagnosis of multiple clonal hematological neoplasms in the same patient is considered rare, being described for the first time in 1953.<sup>3</sup> Some types of tumors have shown early genetic changes in progenitor cells ref.

The molecular mechanisms for the development of MPN remained quite unclear until 2005 when a single point mutation was detected in the gene encoding JAK2. This mutation - the JAK2V617F - is located in exon 14 and is found in almost all patients with PV, in 60% of those with essential thrombocythemia or primary myelofibrosis.<sup>3</sup> The JAK mutation has also been observed in lymphoproliferative diseases. These findings led to the hypothesis that some genomic changes in hematopoietic stem cell precursors may predispose and may

lead to the development of myeloproliferative neoplasms and lymphoproliferative diseases.<sup>8</sup>

In a study by Vannucchi, et al. 820 patients with polycythemia vera and essential thrombocythemia were followed up for approximately 3.3 years, from 1980 to 2008 with the aim of evaluating the incidence of lymphoproliferative disease. The JAK 2 mutation was present in 508 patients. The development of lymphoproliferative disease occurred during the follow-up in 37 patients (4.5%); of these, 14 had a diagnosis of ET and 23 of PV. Twenty-six patients, 10 with ET and 16 with PV, were diagnosed with a monoclonal gammopathy of undetermined significance; change of high occurrence in the general population. Of the remaining 11, there were four chronic lymphocytic leukemia, five non-Hodgkin's lymphomas and two plasma cell disorders, represented by multiple myeloma and Waldenstrom's disease. Mutational status JAK2 V617F was available in 508 patients, of which 384 were mutated. The results of this study indicate that the risk of developing lymphoproliferative disease is significantly increased in patients with chronic MPN compared with the general population and the risk was significantly higher in patients harboring the JAK2 V617F mutation than in the wild type.<sup>3</sup>

In an article published in 2018 by Porpaczy et al. of 626 patients with MPN (216 myelofibrosis) between 1997 and 2016, 69 patients with MPN received JAK1/2 inhibitors (Ruxolitinib, Gandotinibe, Fedratinibe, Momelotinibe) since 2009. Lymphoma developed in three (9.68%) using Ruxolitinib and in 1 (0.54%) among 185 conventionally treated patients.<sup>7</sup> All 4 had mutated JAK 2. The lymphomas were aggressive type B cells and occurred in extranodal sites. The time from the beginning of the treatment with inhibitors until the diagnosis of the lymphoma was from 13 to 35 months (median of 25 months), considered short for a second malignancy. An increase in the prevalence of monoclonal B cell infiltration in previously untreated MPN was also observed.<sup>9</sup>

In a recent study from 2020, 97 patients with myeloproliferative neoplasia and associated lymphoproliferative disease did not use Ruxolitinib, which shows that there may be this association among diseases and not necessarily associated with an increased incidence due to the use of JAK inhibitors.<sup>8</sup> However, large prospective studies are needed to approach this.

Thus, sporadic cases of lymphoproliferative diseases, indolent or aggressive, have been reported in association with myeloproliferative neoplasms. This association has been greater in patients with the JAK2 mutation, but the association of Ruxolitinib or other JAK inhibitors remains uncertain, despite appearing to be a trigger for patients with genetic predisposition. The frequency and possible causes remain uncertain.

## Conflicts of interest

The authors declare no conflicts of interest.

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