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Lenalidomide Treatment in Myelodysplastic/ Myeloproliferative Neoplasms: A Case Report and Review of the Literature

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Abstract **Case Report**

Myelodysplastic/ myeloproliferative neoplasm with ring sideroblasts and thrombocytosis is a rare overlap syndrome, no formal guidelines for the management of this disease exist. We report the case of a 64 years old male patient who was admitted for myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis with mutation in the Janus Kinase 2 gene and hyperdiploid clone. Lenalidomide given for a period of 6 months performed to maintain a normal blood platelet count with, for the first time, sustained platelet response 24 months after discontinuation of treatment.

Keywords: Myelodysplastic / myeloproliferative neoplasm, ring sideroblasts, thrombocytosis, lenalidomide.

INTRODUCTION

Refractory anaemia with ring sideroblasts and thrombocytosis is a rare entity and is defined as an overlap syndrome with clinical and morphologic features of both myelodysplastic syndrome (MDS) and myeloproliferative neoplasm (MPN), including marked thrombocytosis associated with anemia and mutations in the Janus Kinase 2 gene (JAK2) [1, 2]. It was created as a "provisional" entity amongst the group of myeloproliferative/ myelodysplastic crossover syndromes in the 2008 World Health Organization (WHO) classification of myeloid neoplasms [3], then becomes the MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) in the 2016 WHO classification and constitutes a full-fledged entity [4].

There is no consensus on the optimal treatment for this disorder, since cytoreductive therapy with the advantage of reducing thrombocytosis might result in a worsening of anemia and increases transfusion requirement, lenalidomide has proven its effectiveness in some cases [5-8]. We report here the response to lenalidomide for a patient with SMD/SMP-SC-T with a JAK2 V617F mutation and hyperdiploid clone, and his evolution during a period of 24 months after discontinuation of lenalidomide.

OBSERVATIONS

In January 2014, a 64-year-old man with a prior medical history of hypertension complicated by moderate chronic kidney disease, was admitted for normocytic macrocytic anemia (mean corpuscular volume 102 fL; hemoglobin 67 g/L) and thrombocytosis (988 10^9/L). Physical examination revealed mucocutaneous pallor, and no tumoral syndrome was appreciated.

Peripheral blood examination showed normal red blood cell morphology, normal platelet morphology, and normal differential leukocyte count. After confirming persistent thrombocytosis on peripheral blood smear review, our diagnostic evaluation focused on determining whether this process was reactive or clonal. C-Reactive Protein (CRP) and other acute phase reactants were evaluated, results were within normal ranges. Ferritin level was elevated (consistently greater than 2000 µg/L), folate and cobalamine level was normal. Due to known renal pathology, persistent elevated value of creatinine was present (creatinine clearance evaluated at 55 mL/min/1.73 m² according to Modification of Diet in Renal Disease (MDRD)). Hyperuricemia (91 mg/l) was also present.

Initially, the diagnosis of essential thrombocythemia was mentioned, bone marrow aspiration was performed, it showed increased cellularity, erythroid hyperplasia (49%) and marked dyserythropoiesis. megakaryocytes were also greatly increased with atypical features, multilineage dysplasia was present with 2% blasts. Prussian blue iron stain showed 77% of ring sideroblasts (figure 1).

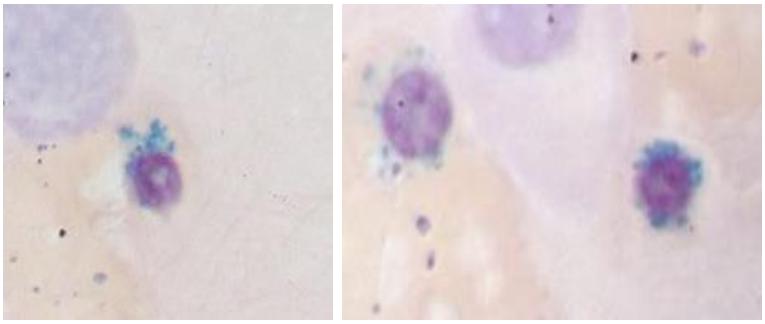

Fig-1: perl's staining of a bone marrow smear showing ringed sideroblasts

Cytogenetic analysis showed the presence of two clones: a normal clone and a second minority clone of cells with hyperdiploïdy. allele-specific polymerase chain reaction (PCR) method revealed the presence of JAK-2 V617 mutation, wich was estimated at 28,11% of JAK2 alleles. A diagnosis of MDS/MPN-RS-T according to the 2016 WHO criteria was established.

Initially, Antiplatelet therapy was started at 75 mg daily, and lenalidomide at 5 mg daily (dose adjusted to renal function), the re-evaluation after 6 months has demonstrated a good platelet response, this treatment was interrupted after 6 cycles. Currently, the patient has a platelet response that lasts more than 24 months without treatment.

Anemia was unsuccessfully treated with erythropoietin and the patient had a *transfusion requirement* of 2 units of red cell concentrates (RCC) bi-monthly, which was complicated by chronic iron overload requiring the use of iron chelation.

DISCUSSION

MDS are often opposed in their biological presentation to MPN. The firsts are readily characterized by cytopenias, due to dysplastic maturation and Excess of apoptosis, while proliferation of one or more hematopoietic cell lineages is common in the seconds. Despite this apparent difference, some disorders associate these two aspects. Thus, beside the categories « MDS » and « MPN », WHO recognizes a mixed category in which we find atypical chronic myeloid leukemia (aCML), chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), and a so-called unclassifiable subcategory of Pathologies presenting myelodysplastic features associated with a proliferative aspect but not meeting the criteria of previous entities [1].

Within this unclassifiable MDS / MPN subcategory, a recurring biological aspect, showing characteristics of refractory anemia with ring sideroblasts and thrombocytosis, posed a problem for WHO experts. In the absence of data that could definitively decide on the nosology of this state, a "provisional" entity was created: refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T) [3]. The provisional entity RARS-T of the WHO 2008 classification has been accepted as a full entity, now termed MDS/MPN-RS-T in the 2016 revision [4]. It remains a rare entity posing a therapeutic dilemma, as the use of cytoreductive therapy to reduce thrombocytosis leads to worsening of anemia and increases transfusion requirements in RCC with installation of secondary hemochromatosis which is difficult to treat.

Our patient meets the 2016 revised diagnostic criteria of the WHO classification concerning the MDS/MPN-RS-T [4] which are: thrombocytosis ≥ 450 G/l associated with anemia and multilineage dysplasia in the BM, ≥ 15% ring sideroblasts in the BM, < 1% blasts in PB and < 5% blasts in the BM, no preceding history of MPN, MDS, or other type of MDS/MPN. Median age at MDS/MPN-RS-T onset is around 75 years [9, 10], this patient was 64 years old at diagnosis.

Cytogenetic abnormalities are rare in MDS/MPN-RS-T (80% of patients have a normal karyotype) [10, 11], our patient had a hyperdiploid minority clone in the karyotype. Clonality analyses and gene expression profiling suggest that MDS/MPN-RS-T is a myeloid neoplasm with both myelodysplastic (refractory anemia with ring sideroblasts-like) and myeloproliferative (essential thrombocythemia-like) features and that it may develop from a preexisting refractory anemia with ring sideroblasts through the acquisition of somatic mutations of *JAK2*, *MPL*, *CALR*, or other as-yet-unknown genes [11]. This mutation of JAK2 characteristic of MPN, also found in our patient, is predominant in MDS/MPN-RS-T (60% of cases) more than other myelodysplastic/ myeloproliferative overlap syndromes [2]. We also find less frequently MPL W515K and CALR mutation (detected in less than 5% of Cases), confirming the myeloproliferative component of this entity [9, 10]. Mutations in the SF3B1 gene are observed in approximately 88% of patients with MDS/MPN-RS-T, and are highly correlated with the presence of ring sideroblasts in the bone marrow.

Survival in MDS/MPN-RS-T patients was shorter than in essential thrombocythemia patients (median survival 76 months *vs.* 115 months, P<0.001)

but longer than in refractory anemia with ring sideroblasts (median survival 76 months *vs.* 63 months, P<0.001), no difference in survival was noted regardless of the JAK2 mutational status or platelet threshold [12].

This rare disease currently lacks formal guidelines for treatment; the different therapeutic options used in a wide European series include transfusion and the use of erythropoietin in 50.3% and 53% of patients, treatment with antiplatelet drugs in 51,5% and cytoreductive therapy in 32.2% of patients [12]. Our patient maintained a severe anemia with transfusion-dependence at a rate of 4 units of RCC per month despite well-conducted erythropoietin treatment, which was responsible for secondary haemochromatosis.

Lenalidomide is effective in several hematological malignancies including lower-risk MDS with or without del(5q) [13, 14]. These results confirm that lenalidomide suppresses the myelodysplastic clone. Huls *et al*. [5] have published in 2010 the efficacy of single-agent lenalidomide in two MDS/MPN-RS-T patients with a JAK2 V617F mutation, both patients normalized their platelet counts and became transfusion-independent after treatment with lenalidomide, one of them had even a molecular response (no detection of JAK2-V617F mutation by quantitative PCR). In 2013, lenalidomide was given to a patient with an extensive marrow fibrosis and massive splenomegaly [6], it was able to reduce the splenomegaly, but worsened the various cytopenias. Also in 2013, Caers *et al*. treated with lenalidomide a patient MDS/MPN-RS-T with a JAK2-V617F mutation and del(5q), who besides haematological response, showed a molecular response [7]. More recently, in 2015, Nichele *et al*. described a patient with MDS/MPN-RS-T and JAK2 V617F mutation, who reached transfusion independency and good control of platelet count after treatment with lenalidomide [8].

Our patient has a MDS/MPN-RS-T with JAK2 V617F mutation, he received a treatment with lenalidomide for a period of 6 months, which performed, for the first time, to maintain a durable platelet response for 24 months after treatment discontinuation.

These results show that lenalidomide may have good platelet response in patients with MDS/MPN-RS-T and which can extend in the time, other large cohort studies are needed to confirm this finding.

Conclusion

This case exhibits an example of effective treatment of myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis with lenalidomide and shows that, for the first time, platelet response can be maintained 24 months after stopping treatment.

Lenalidomide is a promising treatment option for those affected by MDS/MPN-RS-T and warrants further investigation in larger clinical trials.

The authors declare that they have no conflict of interest.

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