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Case report/Kazuistyka

The patient with 5q minus syndrome and *JAK2* V617F mutation with the presence of ringed erythroblasts meeting the criteria of RARS-T effectively treated with lenalidomide – A case report

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ABSTRACT

5q minus syndrome is a form of myelodysplastic syndrome characterized by the presence of an isolated deletion of long arm of the chromosome 5. Patients with 5q minus respond well to the treatment with lenalidomide. The presence of the *JAK2* V617F mutation is a common feature of refractory anemia with ring sideroblasts and marked thrombocytosis. Much less is known about effectiveness of lenalidomide in these patients. We present the patient with 5q minus syndrome and *JAK2* V617F mutation accompanied by the presence of ringed erythroblasts meeting the criteria of RARS-T. We could identify only two such patients reported in the literature; no details were given about effectiveness of lenalidomide in that group. We observed good response to the treatment with lenalidomide with transfusion independence 9 months after starting of the treatment; however, there was no complete eradication of del (5)(q13q31) clone nor the clone with *JAK* V617F mutation.

Introduction

5q minus syndrome (5q minus) is a form of myelodysplastic syndrome (MDS) characterized by the presence of an isolated deletion of long arm of the chromosome 5 [1]. The disease has a relatively good prognosis, the overall survival rate is estimated at approximately 145 months and the risk of transformation to acute myeloid leukemia is less than 10% [2, 3]. In a small percentage of cases, patients with

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5q- syndrome may exhibit *JAK2* V617F mutation [4]. The authors of the fourth edition of WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues (WHO 2008) separated *JAK2* V617F mutated form that emerged from the typical 5q minus syndrome. In their opinion, there is not enough data collected for accurate classification of this subgroup. It was decided that temporarily the diagnosis should be classified as MDS, not as a myeloproliferative disease, with the addition of information about the presence of the *JAK2* V617F mutation [5, 6]. On the other hand, the presence of the *JAK2* V617F mutation is a common feature of refractory anemia with ring sideroblasts and marked thrombocytosis (RARS-T), which was included into "Myelodysplastic/myeloproliferative neoplasm, unclassifiable" as a provisional entity grouping together patients with the diseases having features of myelodysplastic and myeloproliferative disease [7, 8]. Patients with 5q minus syndrome usually respond well to the treatment with lenalidomide [9–11]. Much less is known about its effectiveness in the patients meeting the criteria of RARS-T [12, 13]. In this paper, we present the case of a patient with 5q minus syndrome with *JAK2* V617F mutation features and ringed erythroblasts accompanied by thrombocytosis effectively treated with lenalidomide.

A case report

A 59-year-old female patient was admitted to the department of hematology due to persistent macrocytic anemia with hemoglobin 9.9 g/dl (mean cell volume – MCV – 104.3 fl), white cell count 9.50 G/l, and with platelet count 944 × 10^9/l. Before she was referred to a hematologist, she had been unsuccessfully treated with vitamin B12. At the time of her first presentation, the bone marrow showed 60% cellularity with numerous dysplastic megakaryocytes presenting large hypolobated nuclei and with features of erythroid dysplasia (Fig. 1). Ringed sideroblasts accounted for 18% of her erythroid precursors (Fig. 2). Blast cells expressing CD34 antigen accounted for approximately 3% of

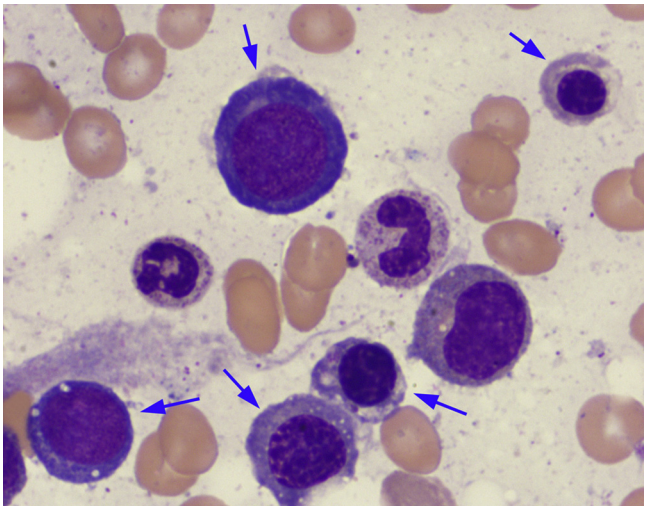

Fig. 1 – Five erythroblasts (arrows), at different stage of maturation, show dysplastic features (megaloid changes, cytoplasmic vacuoles, irregular shape of nucleus, abnormal hemoglobinisation)

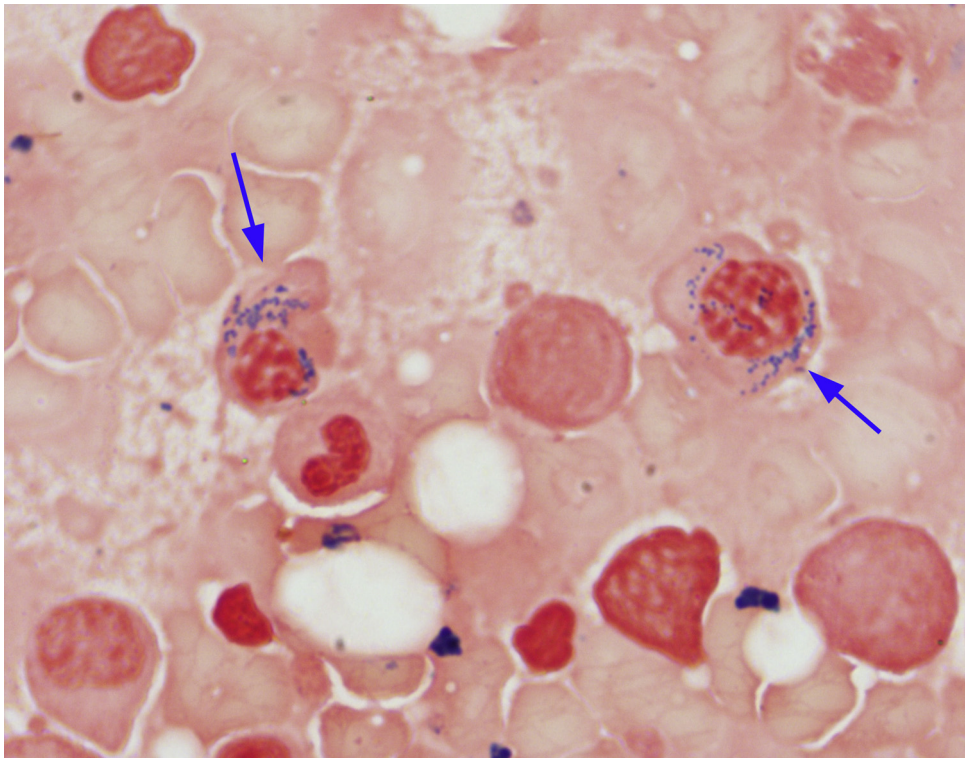

Fig. 2 – Two ringed sideroblasts (arrows)

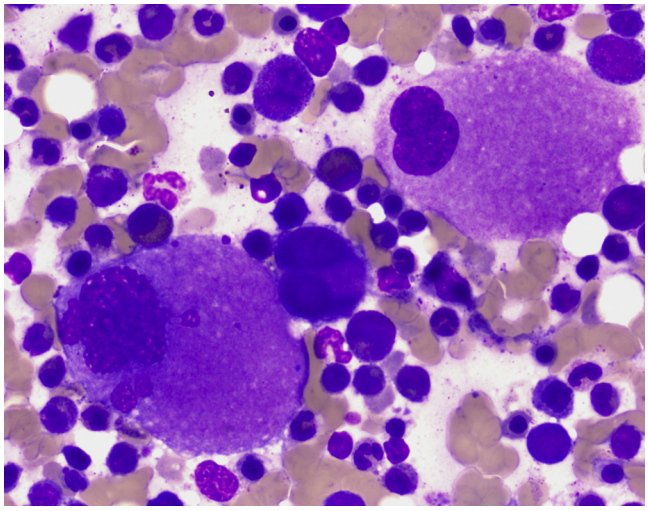

Fig. 3 – Two large hypolobated and one smaller, bi-nuclear, immature megakaryocytes

all nucleated cells and numerous megakaryocytes were present, including some with hypolobated nuclei (Fig. 3). The cytogenetic analysis revealed a deletion of the long arm of chromosome 5: 46, XX, del (5)(q13q31) [13]/46, XX. PCR studies did not show the presence of the *JAK2* V617F mutation at that time.

Once the diagnosis was established, the patient remained under observation, with a sporadic, intermittent requirement of a blood transfusion, and required occasional blood transfusions. After 21 months of follow-up outpatient monitoring, significant worsening of the anemia was noticed and it was decided to commence the treatment with lenalidomide. At that time, the biopsy showed 70% marrow cellularity with large, dysplastic megakaryocytes, and dyserythropoiesis. No increase in blast percent was found. At this point, the PCR test revealed the presence of *JAK2* V617F mutation for the first time.

Lenalidomide therapy was introduced, initially at a dose of 10 mg per day, later reduced to 5 mg per day due to neutropenia. After 12 weeks of that treatment an independence from blood transfusions was achieved. The current level of hemoglobin, evaluated 9 months after the treatment was first introduced, is 11.8 g/dl at MCV of 95.7 fl and the platelet count of 126×10^9/L. The lenalidomide treatment is continued at the dose of 5 mg per day. Despite clinical improvements, the 5q (–) clone is still present and the molecular analysis shows the presence of *JAK2* V617F mutation. Dysplastic features also continue to persist in the marrow.

Discussion

The accurate classification of 5q minus syndrome with a *JAK2* V617F mutation is yet not determined, especially in patients with additional presence of ring sideroblasts. The case described above responded well to the treatment with lenalidomide, which is commonly seen in patients with isolated 5q minus deletion MDS but much less often in patients with other types of low grade MDS [9, 13]. It is on the other hand very difficult to compare the response to lenalidomide treatment observed in our patient to similar cases described in literature. In one of the largest studies, 190 patients with 5q minus syndrome were described by researchers from the Mayo Hospital. It represented 1% of over 24 000 unique patient cytogenetic studies performed at that institution between 1989 and 2009. Among them, 78 patients with the 5q minus syndrome were identified. *JAK2* V617F mutation was shown in 5 (6.4%) of them and did not seem to affect the phenotype or prognosis. Only one of the presented cases had additional feature of RARS, similar to that which is observed in our patient [14]. In another study, Szpurka et al. described 146 patients with RARS, 13 carried *JAK2* V617F mutations and only one of them fulfilled criteria of 5q minus syndrome [8]. No separate information concerning the outcome of the patient's treatment was given. Huls et al. described two patients with RARS-t with *JAK2* V617F mutation, who responded to the treatment with lenalidomide, with one of them achieving complete molecular remission [15].

The effectiveness of lenalidomide has also been confirmed in the presented case. Despite the reduction of the initial dose of 10 mg/d to 5 mg per day due to neutropenia, the patient became completely independent of blood transfusions. However, there was no complete eradication of del (5)(q13q31) clone nor the clone with *JAK* V617F mutation. In a study reported by Fenaux et al. among patients with classic 5q minus syndrome, cytogenetic remission was observed in 50% of them treated with 10 mg lenalidomide daily. Yet, only 25% of patients that received a dose of 5 mg per day went into cytogenetic remission [11]. At the present stage, we are not able to find any difference in response to the treatment with lenalidomide between our patient and other cases with isolated 5q minus deleted MDS.

Authors' contributions/Wkład autorów

MK, JC – study design, data collection and interpretation, statistical analysis, manuscript preparation, literature search. KL, MP-S – data collection. AC – manuscript preparation.

Conflict of interest/Konflikt interesu

None declared.

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None declared.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical

Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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