CASE REPORTS

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Myelodysplastic/myeloproliferative neoplasm with t(2;11)(P21;Q23)del(5) (Q22;Q33) but without mixed-lineage leukemia (MLL) rearrangement

Mijelodisplazna/mijeloproliferativna neoplazma sa t(2;11)(P21;Q23)del(5) (Q22;Q33) ali bez *mixed-lineage leukemia* (MLL) rearanžmana

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Abstract

Introduction. Myelodysplastic/myeloproliferative neoplasms represent a group of rare hematologic malignancies with concomitant characteristics of two different disorders. There are cytopenias and cytoses with dysplastic morphology in the circulating blood and hyperplastic bone marrow, respectively. Many cytogenetic and molecular features have been found in this rare entity, but t(2;11)(p21;q23)del(5) (q22;q33) has not been described so far. **Case report.** We present a patient with myelodysplastic syndrome, subtype refractory anemia without ringed sideroblasts, with unique translocation t(2;11)(p21;q23) associated with del(5)(q22;q33) in the karyotype. Fluorescence *in situ* hybridization analysis did not detect mixed-lineage leukemia (MLL) rearrangement, which can be found in other hematologic malignancies with this translocation. After a year on supportive treatment with packed red cells, thrombocytosis developed with a concurrent increase in white blood cells and the Janus kinase-2 gene mutation. This confirmed the presence of myelodysplastic/myeloproliferative neoplasms. Due to the high platelet count, the cerebrovascular insult has occurred. The patient was treated supportively and with lenalidomide. After introducing the lenalidomide steadily, the patient's condition improved, the peripheral blood count normalized, and he became transfusion independent. **Conclusion.** Patients with the cytogenetic finding of t(2;11)(p21;q23) associated with del(5)(q22;q33) but without MLL rearrangement and with Janus kinase-2 gene mutation presence, respond to lenalidomide therapy and have relatively longer overall survival.

Key words:
myelodysplastic syndrome; thrombocytosis; myeloproliferative disorders; janus kinase-2; mutation; antineoplastic agents; lenalidomide; treatment outcome.

Apstrakt

Uvod. Mijelodisplazne/mijeloproliferativne neoplazme predstavljaju grupu retkih hematoloških maligniteta sa istovremeno prisutnim osobinama dva različita oboljenja. U perifernoj krvi postoji citopenija jedne krvne loze uz citozu drugih krvnih elemenata sa displastičnom morfologijom, dok se u koštanoj srži nalazi hiperplazija. Mnoge citogenetske i molekularne osobine su nađene u ovom retkom entitetu, ali t(2;11)(p21;q23)del(5) (q22;q33) do sada nije opisana. **Prikaz bolesnika.** Prikazan je bolesnik sa mijelodisplaznim sindromom, podtip refraktorna anemija bez prstenastih sideroblasta, sa jedinstvenom translokacijom u kariotipu t(2;11)(p21;q23) udružena sa del(5)(q22;q33). Fluorescentna *in situ* hibridizacija nije utvrdila *mixed-lineage leukemia* (MLL) genski rearanžman, koji je inače osobina ove translokacije. Nakon godinu dana lečenja suportivnom terapijom sa koncentrovanim eritrocitima, razvila se trombocitoza praćena porastom belih krvnih zrnaca i prisustvom mutacije gena Janus kinaze-2. To je povrdilo evoluciju refraktorne anemije u mijelodisplaznu/ mijeloproliferativnu neoplazmu. Zbog visokog broja trombocita razvio se cerebrovaskularni insult. Bolesnik je u daljem toku lečen suportivno uz dodatak lenalidomida. Nekoliko nedelja nakon ove terapije, nalaz u perifernoj krvi se popravio i bolesnik je postao transfuziono nezavistan. **Zaključak. Bolesnici sa c**itogenetskim nalazom t(2;11)(p21;q23) udruženim sa del(5)(q22;q33), ali bez MLL rearanžmana, uz prisustvo mutacije gena Janus kinaze-2, povoljno odgovaraju na lečenje lenalidomidom i imaju relativno duže ukupno preživljavanje.

Ključne reči:
mijelodisplastički sindromi; trombocitoza; mijeloproliferativni poremećaji; janus kinaza 2; mutacije; antineoplastici; lenalidomid; lečenje, ishod.

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Introduction

Myelodysplastic syndrome (MDS) represents a heterogeneous group of diseases characterized by impaired haematopoiesis, dysplasia in one or more myeloid cell lines, and cytopenias in the peripheral blood. In 30% of patients, the disease progresses to acute myeloid leukemia (AML). MDS may be occasionally associated with thrombocytosis and most frequently myelodysplastic/myeloproliferative neoplasms (MDS/MPN). According to the 2016 World Health Organization (WHO) classification, MDS/MPN includes chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (aCML), juvenile myelomonocytic leukemia (JMML), MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)[1–3]. The incidence of MDS/MPN-RS-T is not well known, but it is estimated to be around 5% of all myeloid malignancies [4].

Cytogenetic abnormalities are found in around 50% of patients with MDS, which are significant for classification and prognostic stratification of the disease [5, 6]. Cytogenetic abnormalities in MDS are among the most valuable independent prognostic factors included in the International Prognostic Scoring System (IPSS), which assigns four risk categories of death or transformation to AML. This system is also based on a score that reflects the percentage of bone marrow blasts and the number of cytopenias [5]. However, due to the profound cytogenetic heterogeneity, the impact of many rare cytogenetic abnormalities in a substantial portion of patients with MDS is still unknown and can only be delineated on the basis of larger international studies [5].

In the literature, there are at least 26 cases with t(2;11)(p21;q23) described in MDS [7–9]. This translocation was most frequently associated with del(5q).

We describe a rare case of refractory anemia (RA) with t(2;11)(p21;q23) del(5)(q22;q33) in the karyotype. The erythroblasts did not display rings on Pearl's staining. The patient developed MDS/MPN-T with thrombocytosis and JAK2V617F mutation.

Case report

A 58-year-old male patient presented with malaise, fatigue, and headache starting at the end of 2015. MDS subtype of RA was diagnosed. The patient had an earlier history of hypertension. Upon examination, he was pale but without organomegaly and haemorrhagic syndrome. Complete blood count (CBC) at the time of diagnosis was the following: white blood cells (WBC) 5.57×10^9/L (55.3% segmented neutrophils, 8% monocytes, 1.3% basophils, 3.4% eosinophils, and 32% lymphocytes). Hemoglobin (Hb) was 69 g/L, red blood cells (RBC) 1.88×10^{12}/L, MCV121 fl, platelets 403×10^9/L. The C reactive protein (CRP) and other acute phase reactants were within normal ranges. The renal and hepatic function tests, lactate dehydrogenase (LDH) were normal. The concentration of vitamin B_{12} was 234 pmol/L, iron 17.9 μmol/L (normal range 11–30 μmol/L), and ferritin 409 μg/L (normal range 20–250 μg/L) with total iron-binding capacity – TIBC 42.5 μmol/L (normal range 44.8–80.6 μmol/L). The bone marrow aspirate showed increased cellularity, with slightly reduced megaloblastic erythropoiesis and normal granulopoiesis. Megakaryocytic lineage was profuse with some atypical mononuclear megakaryocytes and rare micromegakaryocytes. There were no manifestations of erythroid dysplasia, and ring sideroblasts were not found. The bone marrow trephine revealed 80% of hematopoietic cellularity with partly megaloblastic erythropoiesis. The ratio of myeloid to erythroid cells was normal with normal myelopoiesis. The megakaryocytes were increased in number showing hypolobulated nuclei. Their cytoplasm stained positively with periodic acid-Schiff (PAS). There were infrequent micromegakaryocytes. The cytogenetic analysis showed aberrant complex karyotype: 46,XY,t(2;11)(p21;q23),del(5)(q22;q33) in twenty mitoses (Figure 1). Fluorescence *in situ* hybridization did not detect mixed-lineage leukemia (MLL) rearrangement (Figure 2).

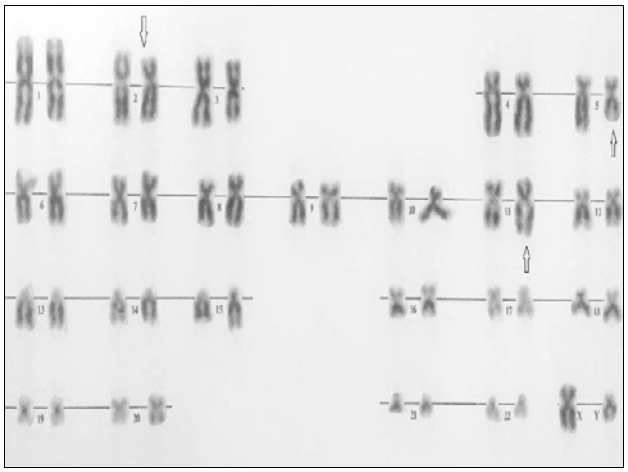

Fig. 1 – Karyotype showing 46,XY,t(2;11)(p21;q23),del(5)(q22;q33).

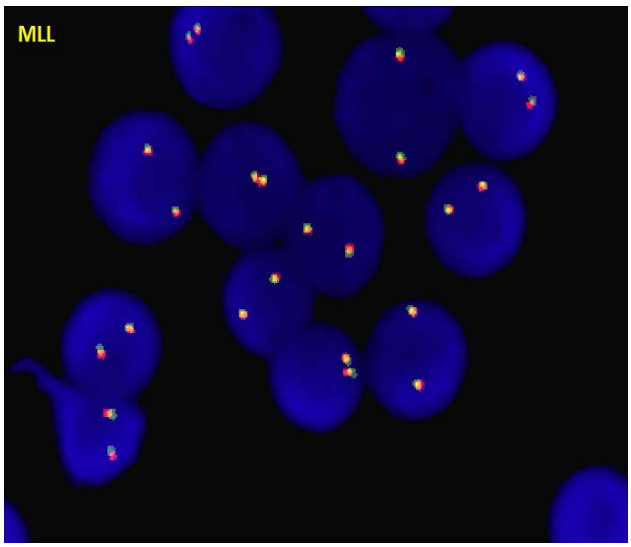

Fig. 2 – Fluorescence *in situ* hybridization – the mixed-lineage leukemia (MLL) gene rearrangement was negative.

The patient was transfusion-dependent and sporadically received twenty units of packed RBC by September 2016. The level of ferritin doubled 891 ug/L, and the erythropoietin level was 1,081 mlU/mL (normal range 3.70–31.50 mlU/mL). In November 2016, his CBC was the following: WBC 7.28×10^9/L (neutrophils 57%, lymphocytes 32%, monocytes 7%, eosinophils 3.1%, basophils 0.9%), Hb 75 g/L, MCV 120 fl and platelets 959×10^9/L. His ferritin increased to 2,710 μg/L. The treatment included folan, danazol, exjade, and prednisone 20 mg/day. The number of platelets and leukocytes increased steadily. Allogeneic bone marrow transplantation was planned, and the HLA typing was duly performed. At that time, no suitable unrelated donor was available. In January 2017, the CBC showed severe anemia, increase in WBC to 15.05×10^9/L with a normal differential. The platelet count was $1,729 \times 10^9$/L and ferritin 3,430 μg/L. The bone marrow histology was hypercellular (80%) with trilineage hematopoiesis with megakaryocytic hyperplasia with solitary or hypolobulated nuclei, some appearing in clusters (up to three cells) with few micromegakaryocytes. A focal paratrabecular dislocation of megakaryocytes existed. The number of blasts was normal (4% of CD34+/CD117+ cells). There was no reticulin fibrosis. On ultrasonography, the spleen was enlarged up to 170 mm in diameter. The treatment with hydroxycarbamide and aspirin was initiated. Unfortunately, the cerebrovascular insult (CVI) had developed. The molecular analysis, using a peripheral blood sample, detected the JAK2 gene mutation (V617F). The laboratory and molecular findings indicated that RA has evolved to MDS/MPN-T. Allogeneic stem cell transplantation has been planned, but a matching donor remained unavailable. Surreptitious supplementation with packed red cells was continued, but the treatment with exjade was irregular because it was financially unaffordable. Consequently, the level of ferritin remained high (4,130 μg/L). The lenalidomide, hydroxycarbamide, danazol, and folan remained his ongoing therapy. Several weeks after introducing lenalidomide, the patient's condition improved. He became transfusion independent, and his blood count in peripheral blood finally normalized.

Informed consent was obtained from the patient for the presentation of this case.

Discussion

The MDS are clonal stem cell disorders that are characterized by dysplasia in one or more myeloid lineages, ineffective hematopoiesis, and one or more cytopenias. In order to define categories within the MDS, the WHO Classification combined clinic, cytology, and cytogenetic analyses [3, 10, 11]. Rarely, certain MDS subtypes present with thrombocytosis rather than cytopenia [2, 3, 10, 12]. The incidence of thrombocytosis in MDS is 5% [9, 10, 13]. The new WHO Classification of the myeloid neoplasms introduced the category of MDS/MPN diseases. These include myeloid disorders, with both dysplastic and proliferative features at the time of initial presentation. This is due to the fact that it was difficult to assign distinctly either of the two features to the myelodysplastic or myeloproliferative group of diseases [10, 11]. Refractory anemia with ringed sideroblasts associated with marked thrombocytosis (RARS-T and MDS/MPN-RS-T), which is occasionally accompanied by increased platelet count, belongs to this category [2].

The presented patient had the clinical, laboratory, and morphologic characteristics of MDS subtype RA without ringed sideroblasts. Initially, the leukocyte and platelet number was normal. Cytogenetic finding showed 46,XY,t(2;11)(p21;q23),del(5)(q22;q33). The patient soon became transfusion-dependent, and after ten months, he was iron overloaded. After one year of supportive treatment, anemia progressed, the number of platelets increased with a concomitant increase in WBC count. The patient developed CVI as a complication. Bone marrow aspiration and biopsy showed hypercellularity, a marked proliferation of hypolobulated megakaryocytes with rare micromegakaryocytes, some focally dislocated to the paratrabecular region. Other signs of myelodysplasia were not in evidence. The spleen size increased to 170 mm, and the odds of essential thrombocythaemia (ET) were considered. However, the cytogenetic abnormality and the presence of micromegakaryocytes were not suggestive of ET. At all times, ringed sideroblasts were not present. The patient progressed from RA to MDS/MPN with thrombocytosis. Using the PCR method, the JAK2-V617 mutation was identified. Hydroxycarbamide was introduced, and the number of platelets dropped.

In the MDS, chromosomal abnormalities are found in about 50% of patients, most frequently as unbalanced structural aberrations and loss of material [5]. Rare cytogenetic abnormalities are observed in MDS with a frequency of less than 2% [5]. In the literature, the translocation of t(2;11)(p21;q23) was found in 26 patients with MDS [7–9]. In approximately half of the published cases, t(2;11)(p21;q23) was associated with deletion of the long arm of chromosome 5, (5q) [7–9]. The translocation breakpoint in 11q23 is near MLL gene. In most of these patients, the examination for the rearrangement of MLL had not been done. In a large cohort study of 1,185 patients with MDS, the presence of t(2;11)(p21;q23) was found in seven patients only. All of the seven patients were males with a median age of 52 years, cytological and histological signs of MDS, and marked dysplasia in megakaryocytopoiesis. Only two patients had a sole t(2;11)(p21;q23), 4 patients had associated 5q deletion, and in one patient, a subclone with deletion 5q was observed. They all lacked the MLL rearrangement. Their median survival was 72 months. It was concluded that t(2;11)(p21;q23) may have a good prognosis [9].

The JAK2 mutation was found in RARS-T in around 58% of cases and 20% of patients with MDS/MPN-RS-T [4, 14]. This mutation in myeloproliferative disorders is accompanied by thrombocytosis and erythrocytosis. In our patient, low numbers of RBC may have been a result of a defect in erythropoiesis. Consequently, an expected "protective effect" of the JAK2 mutation on the erythroid

cell line was suppressed [14, 15]. Similarly, JAK2 positive patients may also have leukocytosis as a result of a proliferative signal to leukocyte precursors [14, 16, 17].

Conclusion

This presentation suggests that specific chromosomal abnormality t(2;11)(p21;q23),del(5)(q22;q33) could be observed in patients with myelodysplastic/myeloproliferative neoplasms, most frequently without MLL gene rearrangement, and in addition with Janus kinase-2 gene mutation, they significantly respond to therapy with lenalidomide. A favorable response of our patient to lenalidomide indicates that the dominant cytogenetic finding in his karyotype was del(5)(q22;q33).

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