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Authors Čolović N *†, Denčić-Fekete M*, Stamatović D‡, Leković D*†, Gotić M*†, Vojnosanitetski pregled (2019); Online First January, 2019.

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Čolović N *†, Denčić-Fekete M*, Stamatović D‡, Leković D*†, Gottić M*†
* Clinic of Hematology, Clinical Center of Serbia, Koste Todorovića 2, Belgrade, Serbia
† Medical faculty, University Belgrade, Dr Subotića 8, Belgrade, Serbia
‡, Military Medical Academy, Clinic of Hematology, Belgrade, Serbia.

Corresponding author:
Doc. Dr Natasa Colovic
Clinic of Hematology
Faculty of Medicine, University Belgrade
Dr. Subotica 8
11010 Belgrade
Serbia.
Tel. +381 11 361 55 69
E-mail address: natasacolovic73@gmail.com
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Abstract

Introduction. Myelodysplastic/myeloproliferative neoplasms represent a group of rare hematologic malignancies colluding the 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 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 the white blood cells and the Janus-kinase 2 gene mutation. This confirmed the presence of myelodysplastic/myeloproliferative neoplasms. Complicating the high platelet number, the cerebrovascular insult has occurred. The patient was treated supportively and with lenalidomide. After introduction of lenalidomide steadily his condition improved, peripheral blood count normalized and he became transfusion independent. Conclusion. The cytogenetic finding of t(2;11)(p21;q23) associated with del(5)(q22;q33) but without rearrangement MLL and in addition with Janus 2 kinase gene, respond to lenalidomide and have relatively longer overall survival.

Key words: myelodysplastic syndrome, thrombocytosis, myeloproliferative neoplasm, Janus 2 kinase gene mutation.

Apstrakt

Uvod: Mijelodisplezne/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 elementa sa displastičnom morfologijom a u kostnoj srži se 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 refraktarna 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 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-kinase 2. To je povrđilo evoluciju refraktarne anemije u mijelodisplaznu/ mijeloproliferativnu neoplazmu. Zbog visokog broja trombocita razvio se cerebrovaskularni insult. Bolesnik je u daljem toku lečen suportivno uz dodatak lenalidomida. Nakon nekoliko nedelja ove terapije našal se u perifernoj krvi se popravio i on je postao transfuziono nezavistan. Zaključak. Citogenetski nalaz t(2;11)(p21;q23) udružen sa
del(5)(q22;q33) ali bez MLL rearanžmana uz prisustvo mutacije gena Janus 2 kinaze povoljno odgovaraju na lečenje lenalidomidom i imaju relativno duže ukupno preživljavanje.

Ključne reči: mijelodisplazni sindrom, trombocitoza, mijeloproliferativna neoplazma, mutacija gena Janus 2 kinaze.

**Introduction**

Myelodysplastic syndrome (MDS) represent 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 progress to acute myeloid leukemia. MDS may be occasionally associated with thrombocytosis and most frequently in myelodysplastic/myeloproliferative neoplasms (MDS/MPN). According to 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). 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 categories of the risk of death or transformation to acute myeloid leukemia (AML). This system is also based on a score that reflects the percentage of bone marrow blasts and 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 patient presented with malaise, fatigue and headache starting by the end of 2015. MDS subtype of RA was diagnosed. He had an earlier history of hypertension. On examination, he was pale but without organomegaly and haemorrhagic syndrome. Complete blood count (CBC) at the time of diagnosis was: white blood cell (WBC) 5.57x10⁹/l (55.3% segmented neutrophils, 8% monocytes, 1.3% basophiles, 3.4% eosinophils, and 32% lymphocytes). The hemoglobin (Hb) was 69 g/l, red blood cells (RBC) 1.88x10¹²/l, MCV 121 fl, platelets 403x10⁹/l. The CRP and other acute phase reactants were within normal ranges. The renal and hepatic function tests, lactate dehydrogenase (LDH) were normal. The concentrations of vitamin B. was
234 pmol/l, iron 17.9 μmol/l (normal range 11-30), and ferritin 409 μg/l (normal range 20-250 μg/l) with 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 manifestation of erythroid dysplasia and ring sideroblasts were not found. The bone marrow trephine revealed 80% 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 PAS. There were infrequent micromegakaryocytes. Cytogenetic analysis showed aberrant complex karyotype: 46,XY,t(2;11)(p21;q23),del(5)(q22;q33) in twenty mitoses. Fluorescence in situ hybridization did not detect MLL rearrangement. He was transfusion dependent and sporadically received twenty units of packed RBC by September 2016. The level of ferritin doubled 891ug/l and erythropoietin level was 1081 mlU/ml (normal range 3.70-31.50 mlU/ml). In November 2016 his CBC was: WBC 7.28x10^9/l (neutrophils 57%, lymphocytes 32%, monocytes 7%, eosinophils 3.1%, basophils 0.9%), Hb 75g/l, MCV 120 fl and platelets 959x10^9/l. His ferritin increased to 2710 μg/l. The treatment included folan, danazol, exjade, and prednisone 20 mg/day. The number of platelets and leukocytes steadily increased. Allogeneic bone marrow transplantation was planned and the HLA typing duly performed. At that time no suitable unrelated donor was available. In January 2017 CBC showed severe anemia, increase in WBC to 15.05x10^9/l with a normal differential. The platelet count was 1729x10^9/l and ferritin 3430 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. There existed a focal paratrabecular dislocation of megakaryocytes. The number of blasts was normal (4% of CD34+/CD117+ cells). There were no reticulin fibrosis. On ultrasonography the spleen enlarged to 170 mm in diameter. The treatment with hydroxy carbamide and aspirin was initiated. Unfortunately, the cerebrovascular insult (CVI) had developed. Molecular analysis, using a peripheral blood sample, detected JAK2 gene mutation (V617F). The laboratory and molecular findings indicated that RA has evolved to MDS/MPN-T. Allogeneic stem cells transplantation has been planned but a matching donor remained unavailable. Surreptitious supplementation with packed red cells was continued but treatment with exjade was irregular because it was financially unaffordable. In consequence, the level of ferritin remained high (4130μg/l). The lenalidomide, hydroxy carbamide, danazol, and folan remained his ongoing therapy. After several weeks of introduction of lenalidomide his condition improved, he became transfusion independent and finally his blood count in peripheral blood normalized.

Discussion

The MDS are clonal stem cells disorders characterized by dysplasia of one or more of the myeloid lineages, ineffective hematopoiesis and by one or more cytopenias. The World Health Organization (WHO) Classification in order to define categories within MDS 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 includes myeloid disorders both those with dysplastic and those with proliferative features at the time of initial presentation because there were difficulties to
distinctly assign either of the two to the myelodysplastic or myeloproliferative group of diseases (10, 11). To this category belong refractory anemia with ringed sideroblasts with marked thrombocytosis (RARS-T) and MDS/MPN-RS-T which sometimes is accompanied by increased platelet count (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). He soon became transfusion dependent and after ten months 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, marked proliferation of hypolobulated megakaryocytes with rare micromegakaryocytes, some focally dislocated to the paratrabeular 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 PCR method 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 in 26 patients with MDS the translocation t(2;11)(p21;q23) was found (7-9). In approximately half of the published cases t(2;11)(p21;q23) was associated with deletion of long arm of chromosome 5 (5q)(7-9). Translocation breakpoint in 11q23 is near mixed lineage leukemia (MLL) gene. In most of these patients the examination for the rearrangement of MLL had not been done. In a large cohort of 1185 patients with MDS the presence of t(2;11)(p21;q23) was found in seven patients only, all were males with a median age of 52 years and cytological and histological signs of MDS and marked dysplasia in megakaryocytopenia. 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).

JAK2 mutation was found in RARS-T in around 58% cases and in 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 defect in erythropoiesis. In consequence, an expected “protective effect” of JAK2 mutation on 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 myelodysplastic/myeloproliferative neoplasms, most frequently without MLL gene rearrangement, and in addition with Janus 2 kinase gene mutation and significantly respond to therapy with lenalidomide. Favorable response
to lenalidomide indicates that dominant cytogenetic finding in his karyotype was del(5)(q22;q33).

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There is no conflict of interests of all authors. This research involves one human participant.

Informed consent was obtained from the patient.

References


Fig 1.
Fig 2.

Legend for the figures

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

Fig 2. Fluorescence in situ hybridization - the MLL gene rearrangement was negative