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Case Report / Приказ болесника

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Rare case of myelodysplastic syndrome with near-tetraploidy and *TP53* mutation

Редак случај мијелодиспластичног синдрома са приближном-тетраплоидијом удруженом са TP53 мутацијом

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SUMMARY

Introduction Chromosomal numerical aberrations are very common in hematological malignancies, but near-tetraploidy (80-104 chromosomes) is rare in myeloid lineage malignancies, with only a few cases reported in myelodysplastic syndrome (MDS). Due to a small number of cases with this rare cytogenetic abnormality, clinicopathological significance of near-tetraploidy in MDS is still unknown.

In this case report we present a case of *de novo* MDS patient with near-tetraploidy in association with *TP53* mutation, and we aimed to elucidate the prognostic significance of this rare genetic feature.

Case Outline In August of 2018 a 71-year-old male presented with severe anemia, thrombocytopenia, and leucopenia and enlarged spleen. Laboratory data were as follows: hemoglobin (Hb) 93 g/L, white blood cells (WBC) 2.8×10^9/L and platelets 23x109/L**.** The bone marrow aspirate was hypercellular, megakaryocytes were not found, granulocytic cells were 15% with signs of dysplasia, with 16% of blast cells without Auer rods. The finding was in correlation with diagnosis of MDS, type RAEB2 which was also confirmed by immunophenotyping. Cytogenetic finding was near-tetraploidy (48,XY+mar[10]/92,XXYY[10]), and *TP53* mutational analysis showed the presence of mutation in exon 8 (p.D281A; c.842 A>C). The patient received from time-to-time packed red blood cells and platelets, and died four months after initial diagnosis.

Conclusion Near-tetraploidy associated with *TP53* mutation has been described only in few MDS cases. Results of these reports including ours suggest that the association of *TP53* mutation and near-tetra polyploidy is a poor prognostic factor.

Keywords: near-tetraploidy; *TP53* mutation; myelodysplastic syndrome; prognosis

САЖЕТАК

Увод Нумеричке аберације хромозома су веома честе код хематолошких малигнитета, али приближне-тетраплоидије (80-104 хромозома) су ретке у малигнитетима мијелоидне лозе, са само неко-лико случајева пријављених у мијелодиспласти-чком синдрому (МДС). Због малог броја случаје-ва са овом ретком цитогенетском абнормалнош-ћу, клиничко-патолошки значај приближне-тетра-плоидије у МДС-у је још увек непознат. Овим приказом случаја *de novo* пацијента са МДС-ом, са приближном-тетраплоидијом и присуством мутације у *TP53* гену циљ нам је био да расветли-мо прогностички значај ове ретке генетске карактеристике.

Приказ болесника Приказан је 71-годишњи болесник који је у августу 2018. године развио симптоме тешке анемије, тромбоцитопеније, леукопеније и увећане слезине. Лабораторијске анализе су показале следеће: хемоглобин 93 g/L, леукоци-ти $2,8\times10^9$/L и тромбоцити 23×10^9/L. Аспират ко-штане сржи је био хиперћелијски, мегакариоцити нису нађени, 15% гранулоцита са знацима дис-плазије, 16% бласта без Ауерових штапића. Налаз је одговарао дијагнози МДС-а, типа RAEB2, што је потврђено и имунофено-типизацијом. Цитоге-нетском анализом утврђено је присуство прибли-жне-тетраплоидије (48,XY+mar[10]/92,XXYY [10]), а анализа мута-ција у *TP53* гену је показала присуство мутације у егзону 8 (p.D281A; c.842 A>C). Пацијент је по потреби примао трансфузију еритроцита и тром-боците, а умро је 4 месеца након почетне дијагнозе.

Закључак Присуство приближне-тетраплоидије удружене са мутацијама у *TP53* гену је описано само у неколико случајева МДС-а. Резултати ових случајева, као и наши резултати, указују на то да приближна-тетраполоидија повезана са при-суством *TP53* мутација представња фактор лоше прогнозе.

Кључне речи: приближна-тетраплоидија; *TP53* мутације; мијелодиспластични синдром; прогноза

INTRODUCTION

Myelodysplastic syndromes (MDS) are a group of clonal hematopoietic stem cell malignancies characterized by ineffective hematopoiesis, bone marrow dysplasia, peripheral blood cytopenia and by intrinsic risk of acute myeloid leukemia (AML) transformation [1]. Chromosomal abnormalities may be numeric and structural and can be found in about 50% of primary MDS and in around 80% patients with secondary MDS after chemotherapy or some toxic agents [2, 3]. Chromosomal abnormalities can vary from a single chromosome abnormality such as monosomy, to a complex karyotype. Numerical abnormality like near-tetraploidy (80-104 chromosomes) is rare in myeloid lineage hematologic malignancies like MDS and it is associated with poor outcome [4]. In addition to pretreatment karyotype being essential for risk stratification and treatment of MDS patients, in recent years the influence of mutations detected in over 89% of cases, has been making its impact on the prognostic stratification model [5]. Mutations in *TP53* gene detected in around 10% of novel MDS cases has been shown to have independent adverse prognostic effect [6].

Here, we report the case of a 71-year-old man diagnosed with MDS, with near-tetraploidy accompanied with *TP53* mutation.

CASE REPORT

The patient 71-year-old man, with a history of diabetes mellitus and hypertension, in August 2018. presented with severe anemia, thrombocytopenia, and leucopenia and enlarged spleen with diameter 159 x 64 mm on ultrasonography. He was admitted at the University Clinical Center of Serbia, Clinic of hematology on under the suspicion of evolution of myelodysplastic syndrome (MDS) in acute myeloid leukemia (AML), ECOG-PS 2, and HCT-IC 1.

Laboratory findings were: hemoglobin (Hb) 93g/L, white blood cells (WBC) $2.8x10^9$/L, platelets $23x10^9$/L (leukocyte formula: segmented 11%, lymphocytes 70%, monocytes 2%, eosinophils 3%, basophils 11%, metamyelocytes 1%, blasts 2%, erythroblasts 7/100 WBC). Biochemical analyses were: glycaemia 9,3 mmol/l, total bilirubin 33 μmol/L, ferritin 547 ng/ml, fibrinogen 5,87 g/L, d-dimer 1,29 mg/L. Virusology, HIV, HbsAg and HCV were negative.

The bone marrow aspirate was hypercellular, megakaryocytes were not found, granulocytic cells were 15% with signs of dysplasia, hypogranular and hyposegmented Pelgeroid-like neutrophil element, with 16% of blast cells, without Auer rods, 40% of blast cells were myeloperoxidase positive, erythroid cell line 62% striking was megaloblastic, with presence of 2 to 3 nucleoli in erythroblasts with signs of vacuolization. The finding was in correlation with diagnosis of MDS, type RAEB 2. Immunophenotyping of bone marrow cells done by flow cytometry, showed positivity for HLA-DR, CD34, CD71, CD38, CD200, CD123, cMPO, clizozime, CD117, CD3, CD22. This results also correlated with diagnosis of RAEB2.

Cytogenetic finding was 48,XY+mar[10]/92,XXYY[10]. Molecular analyses of *SF3B1* and *TP53* gene was done using polymerase chain reaction followed by direct sequencing [7, 8]. The patient was *SFB3B1* negative, but in *TP53* gene we detected a single mutation in exon 8 (p.D281A; c.842 A>C) (Figure 1). The diagnosis of MDS, type RAEB 2 was confirmed with ECOG-PS 2 and HCT-IC 1. The patient was unwilling for intensive treatment with chemotherapy. In further course he received from time-to-time packed red blood cells and platelets. He died in December 2018.

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

DISCUSSION

MDS is a highly heterogeneous group of disorders with numerous genetic aberrations. Cytogenetic findings are important prognostic factor incorporated in almost all prognostic scoring systems. Presence of three or more chromosomal anomalies is regarded as complex karyotype which can be associated with progression of MDS to acute myeloid leukemia. Comparing the karyotype in acute leukemias and MDS, numeric aberrations dominate in MDS while in acute leukemias structural aberrations are dominant. Balanced cytogenetic abnormalities, including reciprocal translocations, inversions and insertions, are prevalent in myeloid leukemias but are uncommon in MDS, in which unbalanced numeric chromosomal abnormalities reflecting a gain or loss of chromosomal material are more prevalent [3].

Numeric chromosomal abnormality near-tetraploidy could be found in 1.2% of acute myeloid leukemia, but only in 0.57% of MDS patients [9, 10]. Tumor suppressor gene *TP53* is located on the short arm of chromosome 17(17p13) [9]. *TP53* gene encodes p53 protein which is main regulator of cellular homeostasis, cellular division, DNA-damage replication and apoptosis [9, 11]. *TP53* overexpression may precede to a change of diploidy to tetraploidy state of the cell population, enabling DNA duplication without cell division leading to polyploidia. Near-tetraploidy associated with *TP53* mutation has been described only in 4 MDS cases [9]. Haase at al analyzed cytogenetic findings in a cohort of 2072 patients with MDS but there was no one patient with near-triploidy or near-tetraploidy karyotype. In a group of 1576 patients with MDS the incidence of near-triploidy and near-tetraploidy was 0.57% [10]. In this cohort the authors have found 9 patients with near-triploidy and near tetraploidy karyotype, but association with *TP53* mutation is not described. Among them 8 had only polyploidy, without other aberrations and one had at the same time complex karyotype. In the group of 979 adult patients with different hematological malignancies, association of *TP53* mutation and near-triploidy or near-tetraploidy karyotype was diagnosed in 4 MDS patients, three with RAEB and

one with refractory cytopenia with multilineage dysplasia (RCMD). Patients with RAEB lived 2, 3, and 6 months while patient with RCMD lived 18 months.

In conclusion, *TP53* mutation are found in 5-20% patients with MDS, more frequent in high-risk group associated with complex karyotype involving chromosome 5, 7 and 17 causing negative impact on prognosis [12, 13]. However, *TP53* mutations are rarely associated with near-triploidy or near-tetraploidy karyotype. Latest research of MDS genomic landscape showed that *TP53* mutations are frequently associated with aneuploidy and chromothripsis, and not with other MDS "driver" mutations, suggesting that for *TP53* mutations, alterations at chromosome level represent cooperating, "second hit" event, driving MDS towards leukemic transformation [14]. Although due to the small number of reported cases, it is impossible to determine the prognostic impact of the combined occurrence of near-tetraploidy and *TP53*mutation, based on our case report, we could speculate that it has a poor impact on the prognosis and outcome of the disease.

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Conflicts of interest: None declared.

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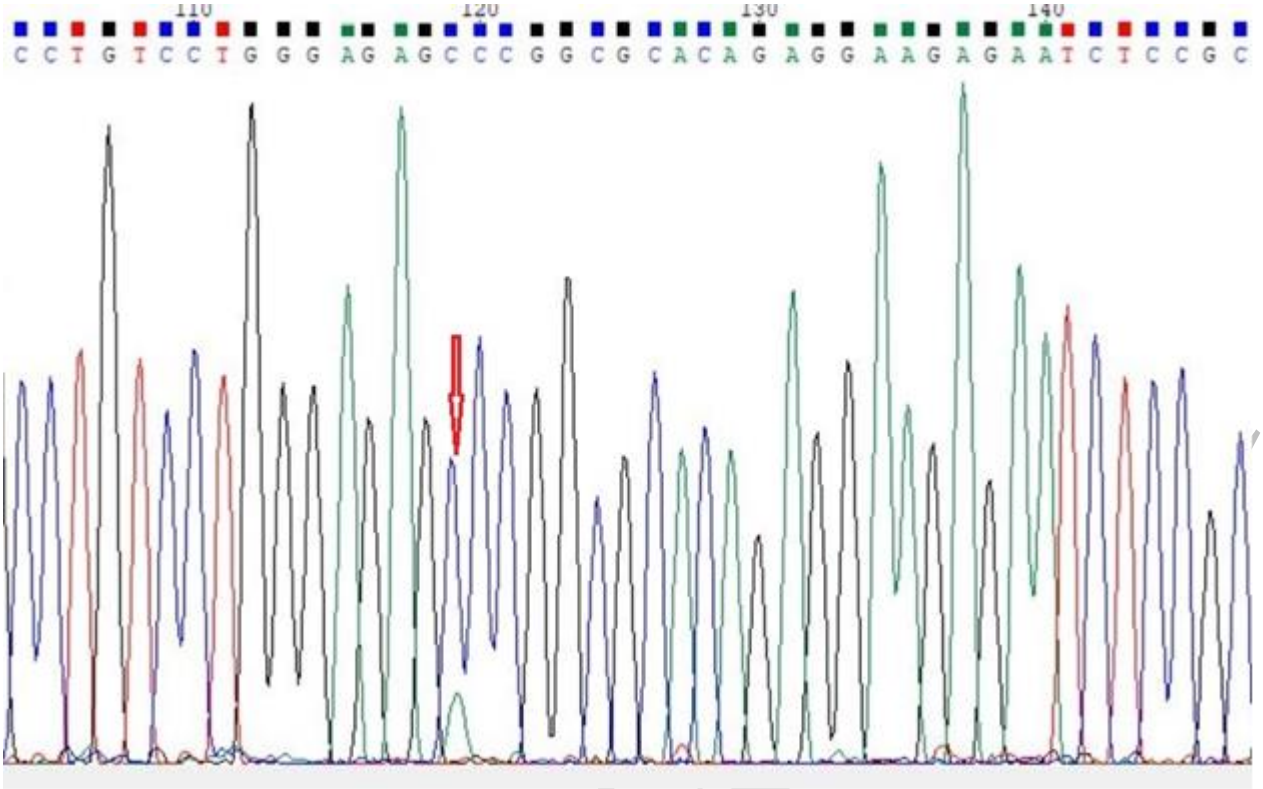

Figure 1. Direct sequencing of exon 8 of *TP53* gen amplified by polymerase chain reaction; the red arrow shows heterozygous, missense mutation at the position 842 (A-green, to C-blue; c.842A>C), resulting in the substitution of amino-acid at the position 281 (Asp to Ala; p.D281A); it has been reported in the COSMIC (Catalogue Of Somatic Mutations In Cancer) data base by number COSM11665

