LETTER TO THE EDITOR
(RESEARCH LETTER)
(CC BY-SA)

UDC: 616.419-07-079.4
DOI: https://doi.org/10.2298/VSP2202204M

Clinical alert: "non-clonal" myelodysplastic syndrome

Kliničko upozorenje: „neklonski" mijelodisplastični sindrom

To the Editor:

We report a peculiar case of a 43-year-old female with a history of chronic moderate neutropenia (WBC range: 2.7-3.4 x 10^9/L, neutrophil range 0.6–0.8 x 10^9/L) lasting for more than five years (first evaluation: November 2014; last follow-up: October 2020). Besides neutropenia, complete blood count was normal as well as detailed biochemical, immunological (rheumatoid factor, antinuclear antibodies, anti-dsDNA antibodies, anti-Sm antibodies, anti-cardiolipin antibodies, and C3/C4 complement levels) and virological testing (HIV, HBV, HCV, CMV, EBV, adenovirus). Bone marrow aspirate was done on two different occasions – in March 2015 and December 2017 and analyzed by two independent hematopathologists. Cytological findings showed normocellular marrow with 20% of megakaryocytes with hypolobulated or "pinball" nuclei. E/G ratio was 1/2.5 with normal morphological appearance of E-lineage. Dysgranulocytopoiesis was moderate (pseudo-Pelger cells, focal or complete hypogranulation in mature cell forms). Blast accounts for 3% of all nucleated cells. Bone marrow trephine biopsy showed normocellular marrow (50–60%) with normal architecture and maturation of all lines. G-lineage was presented mainly with mature forms and excess eosinophils. In addition, two centromedullar nodular lymphoid infiltrates were found. Since such lymphoid infiltrates are common in patients with autoimmune disorders, we performed flow cytometry of lymphocytes from peripheral blood. This analysis showed only a slight reduction of the absolute number of NK-cells and a slight elevation of γδT-lymphocytes. Karyotype of the bone marrow cells was normal (46, XX) in 20 analyzed metaphases. *In vitro* growth of hematopoietic progenitors (CFU-GEMM, CFU-MK, BFU-E, CFU-GM) was normal. Next-generation sequencing testing (MLL Muncher Leukemielabor GmbH), using a gene panel with 63 genes of myeloid and lymphatic diseases, did not reveal any of the tested genes to be mutated. The patient did not have any episode of infection during more than five years of follow-up. In February 2016, a skin lesion localized on the thoracic wall was surgically removed (pathohistological examination showed superficial melanoma, Clarks II, Breslow 0.27mm, pT1b). The oncologist suggested just observation (last follow-up in September 2020).

One of the biggest challenges is separating myelodysplastic syndromes (MDS) from reactive (i.e., nonneoplastic) causes of cytopenia and dysplasia [1], or from a wide and heterogeneous spectrum of the so-called "indolent myeloid disorders" (Table 1) [2]. Demonstration of morphological abnormalities of the bone marrow cells is

Table 1

Spectrum of indolent myeloid hematopoietic disorders (ICUS, IDUS, CHIP, CCUS) in comparison to myelodysplastic syndromes

Feature	ICUS	IDUS	CHIP	CCUS	MDS
Somatic mutation	-	-	+/-*	+/-*	+/-
Clonal karyotype abnormality	-	-	+/-*	+/-*	+/-
Marrow dysplasia	-	+	-	-	+
Cytopenia	+	-	-	+	+

Abbreviations: ICUS – Idiopathic cytopenia of unknown significance; IDUS – Idiopathic dysplasia of unknown significance; CHIP – Clonal hematopoiesis of indeterminate potential; CCUS – Clonal cytopenia of unknown significance; MDS – Myelodysplastic syndromes.
***clonal karyotype abnormality present in ≥ 2 metaphases and/or a somatic mutation present at >2% variant allele frequency (evaluation of mutations should include sequencing of panels incorporating at least 21 most frequently mutated MDS-related genes).**

Correspondence to: Dragomir Marisavljević, University of Belgrade, Faculty of Medicine, 11 080 Belgrade, Serbia.
E-mail: maris@tehnicom.net

still the "gold standard" for diagnosis of MDS as well as cytopenia is a *sine qua non* for any MDS diagnosis [1]. According to the 2016 revision of the WHO classification of myeloid neoplasms and acute leukemia[1], our patient fulfilled diagnostic criteria for MDS with multilineage dysplasia with chronic neutropenia as the most prominent hematological feature. However, the finding of normal *in vitro* growth of hematopoietic progenitors was inconsistent with the presumptive diagnosis of MDS, as we previously reported in a large cohort of MDS patients [3]. In addition, cytogenetic analysis and somatic mutation analysis of genes most frequently mutated in MDS [4] failed to demonstrate the clonal origin of the disease in this patient.

Another very important issue adds to the difficulty of identifying refractory neutropenia as an MDS subtype. Namely, following the publication of the WHO 2008 classification, a study evaluating the inter-observer variability in MDS diagnosis found a discrepancy rate of 27%, mostly in the categories with unilineage dysplasia [5]. However, significant inter-observer variability was not the case in our patient since two additional independent hematopathologists confirmed the preliminary cytological finding. Nevertheless, the diagnosis of refractory neutropenia remains difficult and does not to date reflect an international and reliable consensus on diagnostic criteria.

Taking all these facts into account, what to say to the patient with chronic neutropenia and undoubtful persistent 2-lineage bone marrow dysplasia? Does she have or have not malignant disease called "MDS"? In which cases should the clinician perform molecular testing? What is the most appropriate term for the clinical condition in this patient (i.e., "non-clonal MDS")? So many questions and so many dilemmas.

Dragomir Marisavljević, Andrija Bogdanović

University of Belgrade, Faculty of Medicine,
Belgrade, Serbia

R E F E R E N C E S

1. *Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM*, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016; 127(20):2391–405.
2. NCCN Guidelines Version 1.2020-August 27, 2019. Myelodysplastic Syndromes. http://medi-guide.meditool.cn/ymtpdf/A1721A1C-DA35-3F68-122A-3429A1F100BF.pdf
3. *Marisavljević D, Rolović Z, Sefer D, Basara N, Ilić D, Bosković D, Colović M*. Biological and clinical significance of clonogenic assays in patients with myelodysplastic syndromes. Med Oncol 2002; 19(4): 249–59.
4. *Kohlmann A, Bacher U, Schnittger S, Haferlach T*. Perspective on how to approach molecular diagnostics in acute myeloid leukemia and myelodysplastic syndromes in the era of next-generation sequencing. Leuk Lymphoma 2014; 55: 1725–34.
5. *Font P, Loscertales J, Benavente C, Bermejo A, Callejas M, Garcia-Alonso L*, et al. Inter-observer variance with the diagnosis of myelodysplastic syndromes (MDS) following the 2008 WHO classification. Ann Hematol 2013; 92: 19–24.

Received on March 15, 2021
Revised on September 6, 2021
Accepted on December 30, 2021
Online First January, 2022