Mediterranean Journal of Hematology and Infectious Diseases

Letter to the Editor

Clinical and Prognostic Features in a Young Adult Patient with *de novo* Myelodysplastic Syndrome Presenting t(11;16)(q23;q24)

Keywords: *KMT2A* rearrangement; *de novo* MDS; Conventional cytogenetics; FISH; Prognosis.

Published: January 1, 2022 **Received: September 29, 2021** **Accepted: December 18, 2021**

Citation: Lamim Lovatel V., Otero L., Orlando E.P., Diniz C., Kopischitz Praxedes Lusis M., de Souza Fernandez T. Clinical and prognostic features in a young adult patient with *de novo* myelodysplastic syndrome presenting t(11;16)(q23;q24). Mediterr J Hematol Infect Dis 2022, 14(1): e2022013, DOI: http://dx.doi.org/10.4084/MJHID.2022.013

To the editor.

Myelodysplastic syndrome (MDS) comprises a heterogeneous group of clonal stem cell disorders, characterized by ineffective hematopoiesis, bone marrow (BM) dysplasias, peripheral blood (PB) cytopenias and increased risk of evolution to acute myeloid leukemia (AML). MDS occurs mainly in elderly patients. Reviewing the literature, we notice that chromosomal translocations are rare cytogenetic abnormalities in *de novo* MDS. Therefore, their reporting is essential for identifying new cytogenetic prognostic risk groups and pointing out genes possibly involved in the leukemic transformation.[1-3] Here, we describe a yet unreported t(11;16)(q23;q24) with *KMT2A* rearrangement (*KMT2A*-r*)* in a young adult patient with *de novo* MDS associated with evolution to AML and a poor prognosis.

A 34-year-old male was admitted to National Cancer Institute, Rio de Janeiro in October 2017 with pancytopenia. The myelogram and BM biopsy showed hypercellularity, myeloid hyperplasia with dysplastic cells and 10% of blasts. The diagnosis was MDS with an excess of blasts-2 (MDS-EB-2) according to WHO classification.[3] The patient was indicated to the treatment with a hypomethylating agent, but this drug was not available at the institution at that time. The patient had blood transfusion support and initiated treatment with recombinant erythropoietin (EPO) combined with folic acid, with no response. In May 2018, the myelogram and BM biopsy showed dysplastic cells and maintained 10% of myeloblasts **(Figure 1A-C)**. Immunophenotyping showed 7.7% of myeloid blast cells expressing medium intensity CD45 and CD117+/HLA-DR+/CD34+/CD38+/CD13+ and dysplastic cells **(Figure 1D-H)**. These results confirmed the previous diagnosis of MDS-EB-2.[3] Cytogenetic analysis of BM cells by G-banding showed: 46,XY,t(11;16)(q23;q24)[5]/46,XY[20] **(Figure 1I)**. Fluorescence *in situ* hybridization (FISH) was performed using LSI MLL dual color, break apart rearrangement probe (Vysis, Abbott, USA). FISH analysis showed one allele with a split signal indicating the *KMT2A*-r **(Figure 1J)**. Additionally, the reciprocal translocation was confirmed by using a whole chromosome painting (WCP) probe for chromosome 16 (Vysis, Abbott, USA). No *DNMT3A* mutations were identified within exons 19, 20, 21, 22, and 23.[4] Allogeneic hematopoietic stem cell transplantation (HSCT) was indicated, but no donor was found. Decitabine was initiated with 20 mg/m^2/day intravenous in 1 hour for 5 consecutive days, with cycles of 28/28 days. In November 2018, two months after the fifth cycle of Decitabine, the patient showed improved anemia and thrombocytopenia, although severely neutropenic. In May 2019, the PB count showed: Hb 10 g/dL, platelets 30.000/mm^3, 2.000 WBC/mm^3, 2% of blasts. The BM immunophenotype showed 5% of myeloid blast cells. The FISH analysis demonstrated *KMT2A*-r in BM cells. Three months later, immunophenotyping of PB showed 22% of myeloid blast cells, characterizing the evolution from MDS to AML. The patient was hospitalized and underwent remission-inducing chemotherapy for AML (Cytarabine 100 mg/m^2/EV/day in continuous infusion for seven consecutive days and Daunorubicin at a dose of 60 mg/m^2/day EV on days D1/D2/D3). In February 2020, he was submitted to intensification chemotherapy [Cytarabine 1.5g/m^2/EV/12/12-hours on days D1/D3 and D5, totaling six doses of Cytarabine (2nd intensification cycle)]. No blast cells were observed at PB, but the patient evolved with gradual severe cytopenias. Until April 2020, there was no BM recovery. In June 2020, blood counts revealed an expansion of the leukemic clone, presenting more than 50% of blasts in PB. Treatment with subcutaneous Cytarabine was initiated (200 to 300 mg/week), with no hematological response. Despite all efforts, the patient presented bleeding from the central nervous system in August

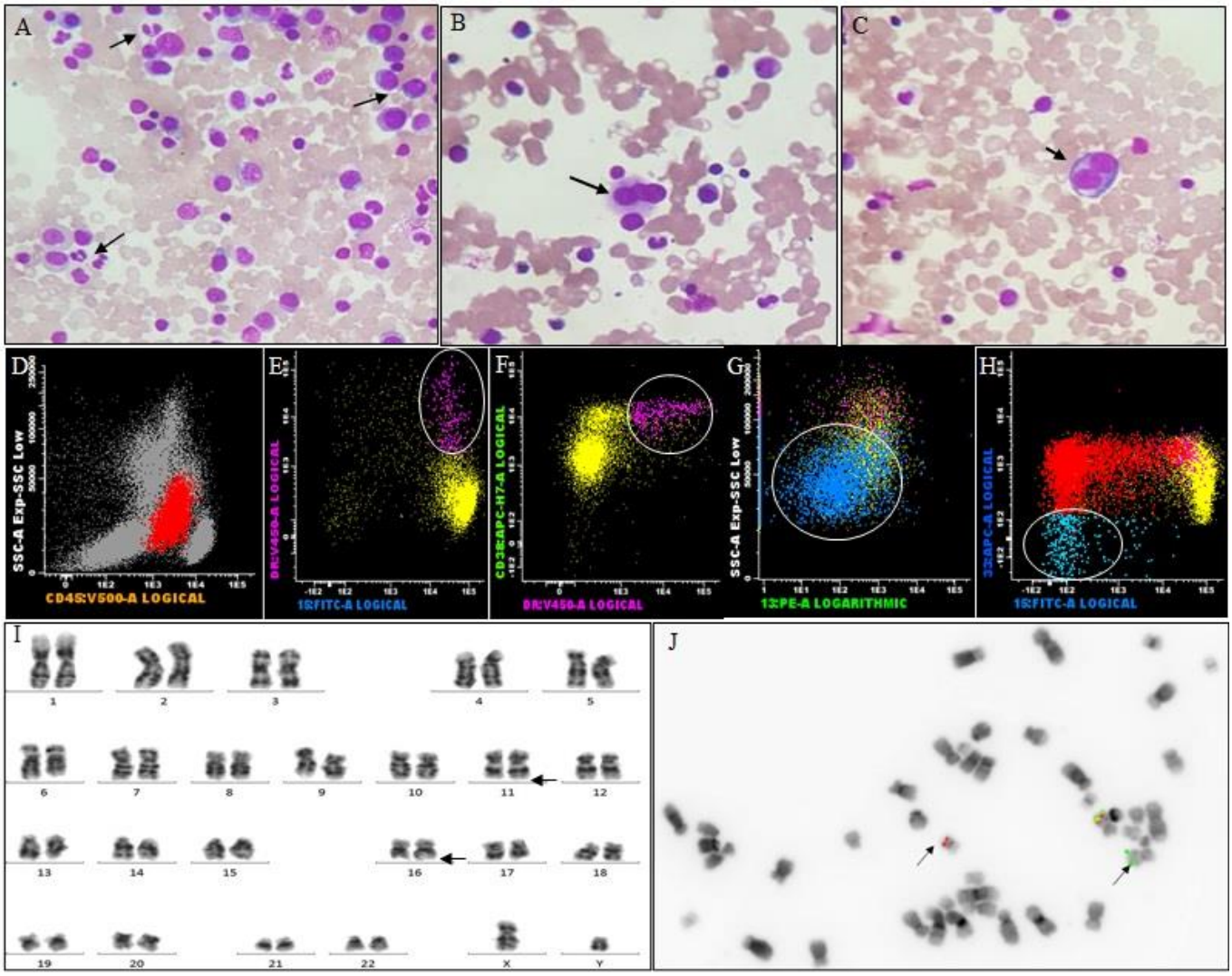

Figure 1. BM analysis in diagnosis: **(A)** Myeloid blast cells (arrows on rigth), neutrophils with pseudo Pelger Huët appearance, typical of MDS (arrows on left). **(B)** Dysmegakaryopoiesis, dysplastic megakaryocyte (arrow); **(C)** Dyserythropoiesis: binucleated eritroblast (arrow). Immunophenotyping of BM cells: **(D)** 7.7% of myeloid blasts (in red) located in the CD45 region of medium intensity and medium complexity; **(E)** Anomalous expression of the HLA-DR marker in part of the neutrophil population; **(F)** Abnormal double expression of CD38 and HLA-DR in part of neutrophils; **(G)** Loss of CD13 expression for monocytic population; **(H)** Loss of CD33 expression in part of the blasts. **(I)** Illustration shows the karyotype 46,XY,t(11;16)(q23;q24) by G-banding. **(J)** FISH analysis of metaphase cell showing the chromosomal rearrangement involving the *KMT2A* gene (11q23 region) and chromosome 16, demonstrated by a split signal in one allele of the *MLL/KMT2A* gene (separated red and green signals).

2020, secondary to treatment-refractory hyperleukocytosis and central leukocytosis, evolving to death. The summary of the steps showing the evolution from MDS to AML is described in **Figure 2**.

In MDS, chromosomal translocations as sole chromosomal abnormality involving chromosome 11 occur in approximately 0.2% of patients.[1] Due to the low number of patients showing 11q23/*KMT2A* translocations in MDS, their real prognostic impact is unknown, and patients with this genetic alteration are assigned to the intermediate-risk group in IPSS-R.[1,2] Our report describes the clinical outcome in a young adult patient with *de novo* MDS showing t(11;16)(q23;q24) with *KMT2A-r*. Considering the age of our patient, some studies in MDS (mainly associated with HSCT) had, in their cohort, patients between 18 and 55 years, therefore including young adult patients.[5] In our patient, the diagnosis of MDS-EB-2 was made according to the criteria of WHO classification.[3] The immunophenotyping analysis showed 7.7% of blasts and dysplastic features in the neutrophil population, monocytic and loss of CD33 in blast cells, characteristics not observed in AML, even with a slower dynamics course.[3] A broad scientific review showed that only four cases of acute leukemia with t(11;16)(q23;q24) had been described so far.[6-9] The patients described with t(11;16)(q23;q24) were associated with leukemia relapse and refractoriness to treatment. In the present study, the patient also had a poor clinical outcome, progressing from MDS to AML and refractoriness to treatment. It is important to note that the hypomethylating agents (HMA) have been considered the standard of care

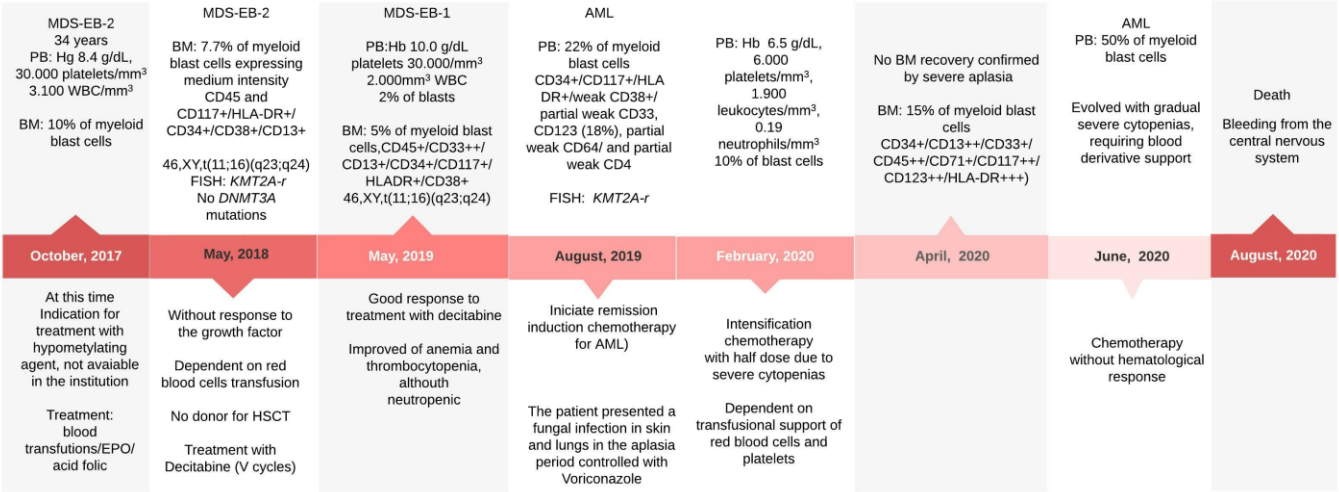

Figure 2. Summary of the steps showing the evolution from MDS to AML.

for MDS patients. However, HMA is not curative. Response to these drugs occurs in approximately 50% of patients, and the duration of response is transient because HMAs do not eradicate neoplastic clones.[10] HSCT remains the only possible curative option for MDS patients.[5,10] This study and literature review highlight the importance of cytogenetics, molecular tests, and clinical follow-up of *de novo* MDS patients to identify new prognostic risk groups and research new therapeutic drugs for these patients. Since this study was the first that described the t(11;16) with *KMT2A*-r associated with AML evolution and poor prognosis in a patient with MDS, it is necessary new studies involving a more number of patients to provide a better understanding of t(11;16) with *KMT2A*-r involved in MDS pathogenesis and its prognosis impact.

Acknowledgments. This study was supported by the Brazilian Ministry of Health (National Institute of Cancer/INCA, Brazil) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq). The authors thank Eliana Abdelhay, Elaiza Kós, Filipe Vicente dos Santos-Bueno and Bruno Almeida Lopes for their technical support.

Authorship and Disclosures. VLL and TSF designed the study and wrote the paper; LO performed the conventional cytogenetics, VLL performed the FISH analysis and the molecular tests; EPO and MKPL attended the patient and collected clinical data; CD performed the immunophenotyping; TSF supervised and reviewed the manuscript. All authors contributed significantly to the work, seeing and approving the manuscript and its submission. The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate. Informed consent was obtained from the case in accordance with the Declaration of Helsinki and this study was approved by the Ethics and Research Committee of National Cancer Institute (reference number # 3401739).

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Competing interests: The authors declare no conflict of Interest.

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