HEMATOLOGY, TRANSFUSION AND CELL THERAPY

www.htct.com.br

Letter to the Editor

When karyotype is decisive for myelodysplastic syndromes diagnosis

ARTICLE INFO

Keywords:
Myelodysplastic syndromes
Karyotype
Diagnosis

ABSTRACT

Introduction: The myelodysplastic syndromes (MDS) are a group of heterogeneous clonal hematopoietic stem cell disorders that results in peripheral blood (PB) cytopenias and bone marrow (BM) dysplasia. Dysplasia is the hallmark of the disorder, and must exceed the threshold of 10%. Conventional karyotype (KT) has a role in the classification and prognostication of subtypes. In daily practice, many cases are diagnosed in face of exuberant clinical complains, but cases with dismal evidences pose real difficulties to definitively conclude the case.

Material and methods: The objective of this study is to detect cases in which no morphology evidence of dysplasia or increased blasts were observed but KT was decisive for MDS diagnosis. 666 cases were admitted to rule out MDS.

Results: There were found 5 (0.75%) cases who presented no evident dysplasia morphology or whose dysplasia was borderline but the karyotype was decisive because showed clonal evidence. The karyotype was: case 1: 46,XY,del(5q)(q13q33),del(11)(q13q23)[7]/46,XY[13]; case 2: 46,XX,del(11)(q21q23)[20]; case 3: 46,XX,del(7)(q22q34)[4]/46,XX[8]; case 4: 47,XX,del(5)(q13q33),+mar[12]/46,XX[8] and case 5: 46,XXt(2;11)(p21;q24),del(4)(?q25),del(21)(q22)[14]/46,XX[6].

Conclusion: Patients with cytopenia and insufficient or borderline evidence of dysplasia may experience a long journey before a MDS diagnosis is made. Cytogenetics studies may abbreviate this pathway when clonal aberrations considered presumptive of MDS are detected. This study shows that karyotype should still be considered as a diagnostic tool.

The myelodysplastic syndromes (MDS) are a group of heterogeneous clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis that results in peripheral blood (PB) cytopenias and bone marrow (BM) dysplasia. There is an increased risk of transformation into acute myelogenous leukemia (AML).

Most patients are diagnosed during routine blood tests or due to symptoms secondary to peripheral cytopenias.

The basis for the diagnosis is the cytomorphological analysis of PB and BM and BM biopsy, according to the WHO classification.[1] The recommended thresholds established for cytopenias are: Hb < 10 g/dL, platelet count <100,000/μL and neutrophil count <1800/μL.[2]

Dysplasia is the hallmark of the disorder, and must exceed the threshold of 10%. The conventional karyotype (KT) has a role in the classification and prognostication of subtypes. Recurrent cytogenetic abnormalities are present in 40–50% of primary cases and up to 80% of those secondary to radio/chemotherapy.

However, when a mild degree of anemia or thrombocytopenia are present, MDS diagnosis may be established if morphology or KT findings are present. Moreover, in cases of refractory or unexplained cytopenia with no morphology evidence of dysplasia or increased blasts, some cytogenetic abnormalities [-7/7q-,5q-,i(17q),t(17p),-13/13q-,del(11q),del/t(12p), del(9q), idic(Xq),

t(11;16),t(3;21),t(1;3),t(2;11), inv/t(3) and t(6;9)] support the diagnosis.

In daily practice, many cases are diagnosed in face of exuberant clinical complaints, but cases with inconclusive evidence pose real difficulties to definitively conclude the case.

Objective

The objective of this study is to detect the frequency of the cases in which no morphological evidence of dysplasia or increased blasts were observed, but the KT was decisive for the MDS diagnosis.

Material and methods

During 2017, we conducted a search at the Fleury database, selecting all cases for which the KT was requested to rule out MDS. All files were reviewed, as well as the PB counts and morphology, BM morphology, immunophenotyping, or molecular tests, by two observers, in a double-blind manner. Bone marrow trephine biopsies were not performed at our institution, so they were not reviewed by us.

Results

A total of 666 cases were admitted to rule out MDS. The only patients selected were those who presented no evident dysplasia morphology or whose dysplasia was borderline, with no increased BM blasts and <15% of ring sideroblasts or abnormal quantity or aberrant phenotypes by multiparameter flux cytometry (IMF). In other words, patients for whom there was not enough dysplasia by morphology or IMF to consider an MDS diagnosis.

Five (0.75%) cases were found, and are described below:

Case 1: A 94-year-old male, who complained of weakness for the last 4 months. Physical examination revealed only paleness. Complete blood count (CBC): Hb 6.5 g/dL; Ht 19%, MCV 116 fL, RDW 22%, WBC: 3010/μL (54-5-1-28-12) and platelets = 51,400/μL. Marrow aspiration was normocellular, G:E ratio = 1.4:1; 2.4% of blasts and no evidence of dysplasia, except for two hypolobulated megakaryocytes among the few that could be observed. Marrow iron was normal and no ring sideroblasts were seen. The IMF presented 1% of immature myeloid cells and did not show aberrations. Karyotype: 46,XY,del(5q)(q13q33),del(11)(q13q23)[7]/46,XY[13]. IPSS-R: intermediary risk.

Case 2: A 63-year-old female, who had presented low platelets and an increased MCV in a routine analysis 6 months early. The physical exam was normal. A complete investigation for secondary thrombocytopenia causes was conducted, but did not reveal any abnormality when a marrow investigation was requested. CBC:Hb 13.7 g/dL, Ht 40%, MCV 98 fL, RDW 13.6%, WBC 2880/μL (51-1-1-37-10) and platelets = 93,000/μL. The marrow aspiration and biopsy were hypercellular and the G:E ratio = 1.4:1, with 2.1% of myeloid blasts and no evidence of dysplasia. The marrow iron was normal and no ring sideroblasts were observed. The IMF presented no aberration. The karyotype presented: 46,XX,del(11)(q21q23)[20]. IPSS-R: very low.

Case 3: A 70-year-old female, who complained of weakness and bruising. The physical examination showed paleness and pethechiae. CBC: Hb 8.4 g/dL, Ht 25.2%, MCV 85.7 fL, RDW 13.6%, WBC 5320/μL (2-1-3-6-44-1-1-38-4) and platelets = 15,000/μL. The marrow aspiration was hypocellular, with 2.8% of blasts, very mild erythroid dysplasia and 7% of ring sideroblasts, inconclusive for an MDS report. An *SF3B1* mutation was further suggested. The karyotype did not present 20 metaphases for analysis due to paucity of sample, but showed 46,XX,del(7)(q22q34)[4]/46,XX[8]; FISH with probes for detecting -5/5q-, -7/7q-, +8, 11q-, 13q- or 20q- confirmed the 7q- in around 20% of interphases. IPSS-R: high-risk.

Case 4: A 91-year-old female, who complained of weakness. The physical examination revealed only paleness. CBC: HB 10 g/dL, Ht 31.2%, MCV 97.5 fL; RDW 23.2%, WBC 4180/μL (37-1-5-47-10) platelets = 150,000/μL. The marrow aspiration and biopsy were hypocellular, with 2% of myeloid blasts, no evidence of dysplasia and generally non-informative; the IMF showed no aberrations and 1% of premature myeloid cells. The karyotype presented: 47,XX,del(5)(q13q33),+mar[12]/46,XX[8]. IPSS-R: low risk.

Case 5: A 75-year-old male presented during the follow-up for a follicular lymphoma treated with radiotherapy 10 months previously the following CBC: Hb = 7.8 g/dL, Ht = 22.9% and MCV = 118.7 fL, RDW = 14.6%; WBC = 3170 (40-12-1-35-12) and platelets: 236,000/uL. The marrow aspiration and biopsy were hypercellular, with 0.4% of blasts without dysplasia. No ring sideroblasts were observed. The karyotype showed: 46,XY,t(2;11)(p21;q24),del(4)(?q25),del(21)(q22)[14]/46,XY[6]. It was classified as t-MDS. IPSS-R: high-risk.

Discussion

Patients with cytopenia and insufficient or borderline evidence of dysplasia may experience a long journey before aMDS diagnosis is made. Cytogenetic studies may abbreviate this pathway when clonal aberrations considered presumptive of MDS are detected. However, when isolated aberrations such as −Y, +8, del(20q) (that have also been described in non-neoplastic conditions) occur without defining morphological criteria, they are not considered as definitive evidence of MDS.

A search in the Fleury database revealed, as expected, a low percentage of cases in which the karyotype aberration was decisive in concluding the diagnosis. Had not the karyotype been requested, these cases would have continued to be investigated, increasing health system costs, as well as delaying diagnostic conclusion.

All patients had a peripheral blood cytopenia, being anemia and thrombocytopenia in two cases, isolated anemia in one and isolated thrombocytopenia in one. Nevertheless, marrow examination did not reveal conclusive dysplasia or aberrations. Fortunately, the karyotype displayed abnormalities that supported the diagnosis. Two out of 5 cases were then classified as low-risk disease.

Gene mutations by next generation sequencing have been introduced as a new tool for the MDS diagnosis and can be interpreted as clonal cytopenias of undetermined significance

(CCUS), except for *SF3B1* in the presence of >5% of ring sideroblasts.

This study shows that the karyotype should still be considered as a diagnostic tool.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Swerdlow SH, Capo E, Harris LN, Jaffe ES, Pileri SA, Stein H, Thiele J, et al. WHO classification; 2017.
2. Greenberg P1, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in MDS. Blood. 1997;89(6):2079–88.

Aline dos Santos Borgo Perazzio [a,b],
Maria de Lourdes L. Ferrari Chauffaille [a,b,*]

[a] *Universidade Federal de São Paulo (Unifesp), São Paulo, SP, Brazil*
[b] *Fleury –, São Paulo, SP, Brazil*

[*] *Corresponding author at*: Universidade Federal de São Paulo (Unifesp), Disciplina de Hematologia, Rua Doutor Diogo de Faria, 824, 5º andar São Paulo, SP CEP: 04023-062, Brazil.
E-mail address: chauffai@terra.com.br (M.L. Chauffaille).

Received 29 November 2018
Accepted 22 March 2019
Available online 14 June 2019
2531-1379/

https://doi.org/10.1016/j.htct.2019.03.004