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Spontaneous chromatid break as clonal evolution in myelodysplastic syndrome patients

Quebra espontânea de cromátides como evolução clonal em pacientes com síndrome mielodisplásica

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ABSTRACT

Myelodysplastic syndrome (MDS) is a clonal hematopoietic stem cell disorder characterized by peripheral cytopenias due to ineffective erythropoiesis and an increased risk for evolving into acute myeloid leukemia (AML). Chromosomal abnormalities represent the most important marker of risk stratification for AML transformation. Chromatid break (chtb) is a discontinuity of a single chromatid. We report the case of a patient with MDS whose cytogenetic analysis showed spontaneous chromatid breakage (chrb): 46,XY,add(13)(q34),chtb(15)(q24)[3]/47,XY,chtb(2)(q22),del(5)(q35),del(7)(q32),+8,del(11q)(q23),del(q22)[cp17]. He was considered a high-risk patient due to the complex karyotype and the presence of chtb. We suggest that this chromosomal abnormality may be considered as a marker of genomic instability in MDS.

Key words: chromosomal breakage; myelodysplastic syndromes; chromosomal instability; genomic instability.

INTRODUCTION

Myelodysplastic syndrome (MDS) is a clonal hematopoietic stem cell malignancy characterized by peripheral cytopenias due to ineffective erythropoiesis and an increased risk of evolving into acute myeloid leukemia (AML)[1]. The identification of chromosomal abnormalities by conventional cytogenetics (G-banding) is important to confirm diagnosis and crucial to determine prognosis and therapeutic approach to MDS. Chromosomal abnormalities are detected in 40% to 60% of MDS patients and represent the most important marker for risk stratification for AML transformation[2].

The presence of mutation in deoxyribonucleic acid (DNA) was detected in up to 80% of the MDS patients[3], many of these DNA lesions are due to increased oxidative stress, which is a common problem in MDS due to the inefficient erythropoiesis and the transfusion dependence[4-7]. Excess of iron is toxic and causes oxidative damage, which predisposes to genomic instability[7, 8].

Unfolding of chromatin structure occurs after DNA damage, so that repair enzymes can access the sites of the lesions. However, these modifications result in a mechanical stress of the chromatin and the chromosome may collapse at specific sites, leading to chromatids break[9]. Chromatid break (chtb) is a discontinuity of a single chromatid in which there is a clear misalignment of one of the chromatids, originating acentric fragments and, consequently generating a misalignment of the chromosome that occurs, mostly, in later S phase and G2 of the cell cycle[10-14].

This type of aberration can be observed in rare autosomal recessive disorder such as Bloom syndrome[10-12] and following exposure to clastogenic drugs such as mitomycin C and bleomycin[10, 15]. The aim of this report is to present a rare case of MDS patient who showed spontaneous chromatid break (chtb) during clonal evolution, and to discuss the possible impact of this finding.

CASE REPORT

A 77-year-old-man sought for medical attendance for malaise and fever. At physical examination, the patient was pale. The patient also reported a history of occupational exposure to solvent. Peripheral blood in the presentation showed hemoglobin 8.1 g/dl, mean corpuscular volume (MCV) = 96 fl, leukocytes 2000/µl (neutrophils 1000/µl) and platelets = 52×10^3/l. Bone marrow aspirate showed

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erythroid dysplasia (> 10%) and micromegakaryocytes. Bone marrow biopsy demonstrated hypercellular marrow with erythroid dysplasia (50% of cells). Cytogenetic analysis showed: 46,XY,del(5)(q31),del(11)(q23)[7]/46,XY[5]. The diagnosis of refractory cytopenia with multilineage dysplasia [(RCMD) – MDS] was established according to the World Health Organization (WHO) classification[16] and the Revised International Prognostic Scoring System (IPSS-R)[17] was intermediate.

The patient has lost follow-up for one year and then presented hemoglobin 5.4 g/dl, leukocytes 2200/µl, neutrophils 1100/µl and platelets 24 × 10^3/l, and became transfusion dependent. At this time, a new cytogenetic analysis was performed and revealed: 46,XY,add(13)(q34),chtb(15)(q24)[3]/47,XY,chtb(2)(q22),del(5)(q35),del(7)(q32),+8,del(11q)(q23),del(q22)[cp17] (**Figure**). He was considered a high-risk patient due to the complex karyotype [according to the International System for Human Cytogenomic Nomenclature (ISCN) 2016] and the presence of spontaneous chtb; he progressed to death after four months.

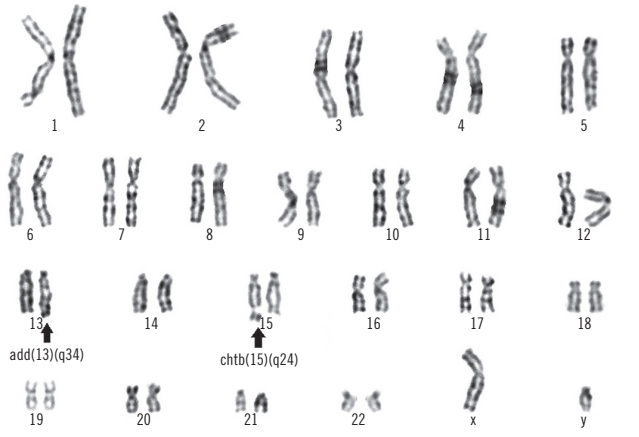

FIGURE – *Cytogenetic analysis after one year without follow-up*

Cytogenetic analysis showed clonal evolution and the presence of spontaneous chromatid break.

DISCUSSION

The chromosomal abnormality detected by G-banding is the most important marker of prognosis in MDS. Patients with complex karyotype and clonal evolution has a high risk for AML transformation[18]. Greenberg *et al*. (2012)[17] confirmed this finding by demonstrating that the cytogenetic abnormality is more predictive of AML evolution than blast counts. The most frequent chromosomal abnormalities in MDS are deletions and aneuploidy involving chromosomes 5, 7 and 8[17, 19, 20]. The reports of chromosomal breakage in MDS have been limited to clastogenic exposure or therapy related MDS [21].

Korgaonkar *et al*. (2008)[15] evaluated 145 MDS cases using cultures of peripheral blood lymphocyte stimulated with phytohemagglutinin and treated with mitomycin C. They reported an increased sensitivity to chromosomal breakage after exposure to clastogenic (mitomycin). We found only one report demonstrating chromosomal breakage in MDS, but limited to centromeric region and detected only by multicolor fluorescence *in situ* hybridization (M-FISH). In this study, the authors attempted to correlate these findings with poor prognosis[21]. To the best of our knowledge, this is the first case of spontaneous chromatid break (chtb) detected by G-banding in MDS.

Vilalba-Campos *et al*. (2016)[22] evaluated the chromosomal abnormalities (by G-band) and the DNA damage (by comet assay) of the peripheral blood lymphocytes from 24 workers exposed to solvents and paint thinners and found a high frequency of chrb among these workers. Chromosomal abnormalities were 3.6 higher in the exposed group when compared to the non-exposed group, indicating a deleterious effect of the aromatic hydrocarbons, such as benzene, present in these solvents[21], suggesting that the presence of chrb is related to the increase of DNA damage.

Our patient became transfusion dependent during the progression of the disease. Massive blood transfusion leads to an iron overload. Iron acts as a cofactor in the production of the hydroxyl radical (•OH), presenting a high reactivity with the DNA molecule, which may induce genomic instabilities and chromosomal breakage[23]. Bryant *et al*. (2010)[24] suggested that the excess of reactive oxygen species (ROS) in leukemic cells leads to the activation of the enzyme Topoisomerase IIα, which is involved in chromatid break formation. In this experiment, they showed that the frequency of chromatid breaks was reduced with reduced expression of Topoisomerase IIα[24, 25].

It is possible that the occupational exposure of solvents and the transfusion dependency that leads to an iron overload and, consequently, ROS increase, may have led to the chromatid break after one-year period. As shown, chromatid break is strongly correlated with the presence of various DNA damages. We suggest that this abnormality is part of a clonal evolution of this patient and, together with the clinical manifestations, led to a poor evolution and death of the patient.

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RESUMO

A síndrome mielodisplásica (SMD) é uma desordem clonal das células-tronco hematopoiéticas caracterizada por citopenias periféricas devido à hematopoiese ineficaz e pelo aumento do risco de evolução para a leucemia mieloide aguda (LMA). As alterações cromossômicas representam o marcador mais importante da estratificação de risco para a transformação de LMA. Quebra das cromátides (chtb) é uma descontinuidade de uma única cromátide. Relatamos o caso de um paciente com SMD, cuja análise citogenética mostrou chtb espontâneo: 46,XY,add(13)(q34),chtb(15)(q24)[3]/47,XY,chtb(2)(q22),del(5)(q35),del(7)(q32),+8,del(11q)(q23),del(q22)[cp17]. O paciente foi considerado de alto risco devido ao cariótipo complexo e à presença de chtb. Sugerimos que essa anormalidade cromossômica possa ser considerada como marcador de instabilidade.

Unitermos: *quebra cromossômica; síndrome mielodisplásica; instabilidade cromossômica; instabilidade genômica.*

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