Case Report

Jumping Translocation in a Patient with Acute Leukemia and Fatal Evolution

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Abstract

Jumping translocations are uncommon cytogenetic abnormalities in which a segment of a donor chromosome, often 1q, is transferred to two or more receptor chromosomes. We describe the case of a 64-year-old man with a history of acute myeloid leukemia associated with myelodysplastic syndrome, who presented with a relapse of the leukemia and, concomitantly, with the appearance of a jumping translocation involving chromosome 1q. The patient had a poor clinical course without the possibility of performing targeted treatment, and he died 5 months after relapse. Jumping translocations are a reflection of chromosomal instability, and they could be related to epigenetic alterations such as pericentromeric chromatin hypomethylation, telomere shortening, or pathogenic variants of the TP53 gene. The existing data suggests a poor clinical outcome, a high risk of disease progression, and an unfavorable prognosis. More molecular studies are required to gain an in-depth understanding of the genetic mechanism underlying these alterations and their clinical significance and to be able to apply an optimal treatment to patients.

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Introduction

Jumping translocations (JT) are rare chromosomic alterations consisting of the nonreciprocal break-off of a segment from a single donor chromosome onto two or more recipient chromosomes. JTs are recurrently observed in solid and hematologic cancers, including myeloid malignancies [1].

To the best of our knowledge, 33 cases of acute myeloid leukemia and 28 cases of myelodysplastic syndrome with JT have been described in the literature to date. The donor chromosome most frequently described is chromosome 1, although the cause of this predilection is unknown. Other donor chromosomes involved are chromosomes 3, 11, 15, and 21. Poor clinical course and disease progression have been observed in patients with myeloid neoplasms carrying JT, although the prognostic implications that these aberrancies may have are not known in depth [2].

Case Presentation

We present the case of a 64-year-old man who was referred to our service in August 2015 because of neutropenia and thrombocytopenia. The patient was asymptomatic, in good general condition, without lymphadenopathy, hepatosplenomegaly, or other findings upon physical examination. The leukocyte count was 3.1×10^9/L (neutrophils 3.1×10^9/L), with hemoglobin of 126 g/L, a platelet count of 95×10^9/L, and 2% blasts. The bone marrow aspirate was diagnostic as myelodysplastic syndrome (MDS) type refractory anemia with excess blasts, RAEB-2 (17% of the blasts of myeloid phenotype), according to the 2008 WHO classification. The cytogenetic study showed poor cellularity, without observable metaphases. Both fluorescent in situ hybridization (FISH) and molecular biology showed no alterations. The prognostic index was high-risk IPSS (int-2). The patient was initially treated with azacitidine, and he was offered a hematopoietic stem cell transplantation from a genotypically identical HLA sister.

After three cycles of azacitidine, the patient was hospitalized for febrile syndrome with marked pancytopenia. A bone marrow biopsy was performed, showing 25% of myeloid phenotype blasts (CD34^{lo}, CD117^{hi}, HLA-DR^{hi}, CD13$^+$, and CD64$^-$), diagnostic of acute myeloid leukemia (AML) with myelodysplasia-related changes, according to the 2008 WHO classification. Cytogenetics was normal, and the WT-1 gene overexpression was demonstrated at the molecular level. The patient was refractory to the induction treatment according to a idarubicin + cytarabine (3 + 7) scheme; therefore, he received a new induction treatment consisting of a FLAG-IDA scheme, achieving complete remission with 2.3% blasts and persistence of multilineage dysplasia.

While waiting for the transplantation, he presented subarachnoid hemorrhage due to aneurysmal malformation with tonsillar herniation, which required embolization, being dismissed for hematopoietic stem cell transplantation.

In June 2016, treatment with azacitidine was restarted. After 29 cycles, in May 2019, pancytopenia was found with 16% blasts in peripheral blood. Bone marrow showed 22.8% blasts of myeloid phenotype (CD34$^+$, CD13$^+$, CD33$^+$, HLA-DR$^+$, CD117$^+$, and CD64$^+$). In the cytogenetic study, a JT was found, with the following karyotype: 46,XY,der(13)t(1;13)(q11;p11)[12]/46,XY,der(15)t(1;15)(q11;p11)[3]/46,X,–Y,+del(1)(p12)[3]/46,X,der(Y)t(Y;1)(q12;q11)[2]. A FISH study with a probe that hybridizes to the TP53 gene was performed, and no deletion of this gene was observed in any of the cells analyzed (200). The molecular biology, performed by next-generation sequencing, detected once more overexpression of the WT-1 gene (33.09%), as well as alterations in the ASXL-1, ETV6, IDH2, SF3B1, and SRSF2 genes, with no mutations in other genes studied, including TP53.

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He received induction treatment with the idarubicin + cytarabine (3 + 7) scheme at reduced doses. In the control bone marrow study (day +28), 6.4% blasts were observed by cytology. At that time, the cytogenetic study showed the following karyotype: 46,XY,der(13)t(1;13)(q11;p11)[11]/46,XY,der(15)t(1;15)(q11;p11)[5]/46,X,der(Y)t(Y;1)(q12;q11)[4]; by next-generation sequencing, in addition to the previous alterations, a mutation in the KMT2A gene was observed, without new findings in TP53. In the subsequent bone marrow re-evaluation (June 2019), refractoriness to treatment was observed, with 40–45% blasts.

Given the progressive AML, without the possibility of active treatment, the patient died 5 months after the finding of JT in November 2019 due to pneumonia.

Discussion

To date, 33 cases of AML and 28 cases of MDS in patients with JT have been observed, with uncertain prognostic significance. In our patient, the donor chromosome was chromosome 1 (at the q11 band level), this being the most frequently described donor chromosome in other published cases [3–7]. It is the longest human chromosome, and alterations in this chromosome are usually found in numerous types of cancer [8].

Several hypotheses have been proposed regarding factors that could influence the mechanism of JT formation, such as chromosomal instability, shortening of telomeres, viral infections, pericentromeric heterochromatin decondensation, or recombination between repeated telomere sequences and interstitial telomeric sequences. The shortening of telomeres in receptor chromosomes (described in JT cases), with the consequent loss of telomeric function, could favor fusion with a donor chromosome, and thus cancer cell proliferation [3, 4, 7, 9].

Sanford et al. [3], in a study of 10 patients, identified frequent chromosome 1 points located in areas related to centromeric DNA (1q10, 1q11, 1p11). Chromosome 1 contains wide areas of constitutive heterochromatin, which can predispose to centromeric instability and fusion processes [8]. Epigenetic modifications, such as the pericentromeric heterochromatin hypomethylation and its subsequent decondensation, could lead to the excision of certain segments of the donor chromosome and fusion with other receptor chromosomes, with associated chromosomal instability [3, 4].

Behrens et al. [2] have also observed that in the receptor chromosomes there is generally a cut point in the pericentromeric or peritelomeric regions, but rarely outside of these locations. In line with other publications, they found significant shortening of telomeres in patients with JT, compared to controls in age-matched groups. Furthermore, in the cases of JT where the cut point of the receptor chromosomes was in the pericentromeric region, there was a pathogenic variant in TP53 (mutations and/or deletions), but not in those with the cut point in the telomeric region. Therefore, Behrens et al. proposed that the pathogenic variants of TP53 may have a role in the formation of JT [2].

In our patient, the involvement of the receptor chromosomes occurred in the pericentromeric region of chromosomes 13 (band p11) and 15 (band p11), and in the peritelomeric region of chromosome Y (band q12). However, there was no TP53 mutation or loss of the 17p13 locus (TP53), and a telomere shortening evaluation could not be performed. All this suggests that more studies are needed to define the impact of these alterations on the generation of JT.

As shown by previous case series, the involvement of receptor chromosomes is highly variable, but the aforementioned receptor chromosomes have been described in other patients, especially chromosomes 13 and 15 [2–5]; other chromosomes frequently involved are chromosome 3, 11, and 21 [2, 3, 8].

In our patient, mutations affecting genes involved in RNA splicing and DNA methylation (ASXL1, SF3B1, SRSF2) were observed [10]. These have been described as frequent "driver" mutations that appear at the beginning of the disease, both in MDS and AML [11, 12]. Furthermore, in AML, somatic mutations in epigenetic regulators have been described in >50% of all cases, being recognized as a key component in leukemogenesis and in JT appearance. These include mutations in ASXL1 and the IDH1/IDH2 family, which are present at the time of leukemia relapse (in our patient, these mutations had not previously been tested before AML diagnosis) [10]. The loss of functionality in the ASXL1 chromatin modifier gene occurs in 10–20% of all AML cases, and it is associated with advanced age, a history of hematologic malignancy, and poor prognosis. A pathogenic variant in position Arg140Gln in the IDH2 gene was detected at the time of relapse, IDH mutations are found in 20% of all patients with AML [13].

In our patient, the appearance of JT was detected 46 and 42 months after the diagnosis of MDS and AML, respectively. Similarly, in recent case series of patients with these neoplasms, a median time of onset of JT of more than 2 years has been observed [3], and within a range of 12 to 39 months from the diagnosis of the malignant hemopathy [4]. These data and those from our case support that the acquisition of JT is a late event in the evolution of the disease, in relation to chromosomal instability and errors in DNA repair, and to disease progression and/or previous treatment [3].

The existing data indicates that patients with malignant blood diseases and JT present a high rate of progression, relapse, and mortality, as well as resistance to treatment. This fact is demonstrated by series of patients with MDS who progressed to AML and relapsed AML, with acquisition of JT (most of them affecting 1q) [3, 4]. Sanford et al. described a median overall survival after JT finding of 9 months (95% CI, 2.5–15.5 months) [3].

In our case, JT implies a complex karyotype, due to the appearance of three concomitant cytogenetic alterations. This itself gives the patient's AML an unfavorable prognosis. Furthermore, we demonstrated the acquisition of an immunophenotypic marker not previously present: CD64. Both findings support the appearance of a new clone in the patient's disease, which favored the refractoriness of leukemia, with a survival of 5 months after relapse.

In conclusion, there are an increasing number of cases described in the literature affected by malignant blood diseases with the appearance of JTs, although they are infrequent alterations. They are associated with a poor prognosis, as in our case. Given the adverse prognosis associated with these chromosomal abnormalities, it is necessary to further investigate the genetic mechanisms involved in their formation. The characterization of the processes involved would have important implications at the clinical level for these patients, requiring new therapies to address these alterations.

Statement of Ethics

The patient's family members have given their written informed consent to publish this case. Information revealing the subject's identity has been avoided.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors have actively participated in the elaboration of the manuscript. It is especially important to highlight their job in the collection of the patient's clinical data during the evolution of the disease, their contribution to the literature research, their interpretation of the different diagnostic tests, and their collaboration in the review of the final version of the article.

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