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New Variant Translocation (8;9;21)(q22;p24;q22) in a Patient with Granulocytic Sarcoma Concurrent with Acute Myeloid Leukemia

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Abstract

Granulocytic sarcoma is a form of acute myeloid leukemia which may occur in any anatomical site. Isolated pancreatic granulocytic sarcoma is however, extremely rare. Translocation t(8;21) is the most common cytogenetic abnormality found in leukemia patients with granulocytic sarcoma and is associated with a relatively good prognosis when treated with chemotherapy. Variants of the t(8;21) are uncommon and account for approximately 3% to 4% of acute myeloid leukemia associated with t(8;21) and are rarely described in acute myeloid leukemia cases associated with granulocytic sarcoma. We report here a patient with acute myeloid leukemia and a novel variant t(8;9;21)(q22;p24;q22) with suspected granulocytic sarcoma in pancreas. A dual-color fluorescence *in situ* hybridization analysis with *RUNX1T1* and *RUNX1* probes, revealed the presence of an *RUNX1/RUNX1T1* fusion signal in this translocation. To the best of our knowledge, a variant of t(8;21) in GS was rarely described and the involvement of the 9q22 region is the first time described here even in isolated AML-M2. We conclude that further accumulation of similar cases is needed and that genetic exploring of variants of t(8;21) may be helpful for a better understanding of molecular pathogenetic mechanism.

Keywords

Granulocytic Sarcoma, AML-M2, t(8;9;21), Conventional Karyotype, FISH, *RUNX1/RUNX1T1*

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1. Introduction

Granulocytic sarcoma (GS) is an uncommon and localized extramedullary tumor composed of immature granulocytic cells. It is also known as extramedullary myeloid tumor or chloroma [1]. It forms a solid malignant tumor consisting of myelocytes or granulocytes and is typically located in bone while occurrence is rare in other parts of the body such as in skin, soft tissue and lymph nodes [2]. The tumor is a rare event of acute myeloid leukemia (AML). GS can occur at presentation, during treatment or in relapse of AML patients. Several chromosome rearrangements were associated with GS, especially t(8;21) and, less often inv(16)(p13;q22). In deed, it is reported in many series of patients with t(8;21) that GS occurs in approximately 18% of this population, which is four times the expected incidence in AML [3].

Molecular characteristics of the (8;21) translocation have been extensively studied. The genes involved in this translocation are the *RUNX*1 (*AML*1) gene on chromosome band 21q22 and the *RUX1T*1 (*ETO*) gene on chromosome band 8q22, leading to formation of a chimeric *RUNX1/RUNX*1*T*1 (*AML*1*/ETO*) fusion gene on the derived chromosome 8 [4]. The fusion protein *RUNX*1*/RUNX*1*T*1 recruits N-CoR, sin3, and histone deacetylases which leads to transcription repression. These mechanisms probably play a contributing role in AML leukemogenesis [5]. Variants of t(8;21)(q22;q22) involving a third or fourth chromosomes are seen in ~4% of AML cases [6]. Patients with these variants show typical features of t(8;21) AML morphologically and, in the limited number of cases examined, the *RUNX*1*/RUNX*1*T*1 fusion transcripts detected were similar to those of t(8;21) [7].

Only few cases of GS of the pancreas had been reported in literatures [8]. We hereby reported a case of suspected GS in the pancreas, in a male patient with AML. Cytogenetic studies showed a complex karyotype including a novel translocation (8;9;21)(q22; p24;q22) in all analyzed cells.

2. Patient and Methods

2.1. Patient

A 60-year-old Tunisian male, with no significant past medical history, was referred to the Aziza Othmana hospital, with a general malaise and leukocytosis. His complete blood count showed an anemic condition, with hemoglobin at 8.0 g/dL, total white blood cell count at 16,700/mm^3, and platelet count at 28,000/mm^3.

Bone marrow (BM) examination showed that 55% of nonerythroid cells were blasts. Immunophenotyping of the blasts cells was positive for HLA-DR (77%), CD13 (59%), CD14 (16%), CD34 (62%), CD65 (27%), CD11c (20%), CD4 (20%), CD56 (7%), CD38 (96%), CD15 (65%), CD117 (30%), CD36 (16%) and cytoplasmic MPO (80%). Thus, the diagnosis was AML, M2 in the FAB system. At abdominal exploration, a mass was found in the pancreatic head suspicious of GS in the pancreas. However, the pathology and immunohistochemistry were not made to confirm the diagnosis. According to these data, the diagnoses of AML-M2 in the FAB classification and suspicious pancreatic GS were made. The patient was treated by low-dose chemotherapy because his general state is too much altered.

2.2. Cytogenetic Analysis of Bone Marrow Cells

BM samples were collected at presentation, referred to our laboratory. BM mononuclear cells were cultured for 48 hours and chromosome preparations were made by an R-banding method. Twenty metaphases from each specimen were analyzed and karyotypes as described previously [9] in accordance with the International System for Human Cytogenetic Nomenclature [10].

2.3. FISH Analysis

A dual-color FISH assay using *RUNX*1*T*1 and *RUNX*1 specific probes (Vysis, Downers Grove, IL) was performed on BM cells, as previously described [11]. The *RUNX*1*T*1 probe was directly labeled with Spectrum Orange, and the *RUNX*1 probe was directly labeled with Spectrum Green. The hybridizations were performed on fixed cell pellets.

After hybridization and washing, cells were counterstained with DAPI (4',6-diamidino-2-phenylindole), then were examined with a fluorescent microscope equipped with appropriate filters and Cyto-Vision FISH system image capture software (ZeissAxioskop 2 plus).

In a normal case, the hybridization with the *RUNX*1*T*1 (orange) and the *RUNX*1 (green) probes showed two

orange and two green signal patterns. However, in a case with the t(8;21), the hybridization with these probes showed one or two fusion signals (orange/green or yellow) corresponding to one or two fusion genes *RUNX*1/*RUNX*1*T*1, one orange and one green signal patterns corresponding to the normal copies of the *RUNX*1*T*1 and the *RUNX*1 genes, respectively.

3. Results

Chromosome study using R-banding technique revealed the involvement of the chromosome region 9p24 in addition to the classic reciprocal translocation between 8q22 and 21q22 in AML-M2. Thus, the karyotype is 45,X,-Y,t(8;9;21)(q22;p24;q22) in 14 analyzed metaphases (**Figure 1(A)**).

Slides contain no metaphases so the interphase FISH analysis for the *RUNX*1/*RUNX*1*T*1 probe showed one normal orange (*RUNX*1*T*1) and one normal green (*RUNX*1) signals on normal chromosomes 8 and 21 and one orange-green fusion signal corresponding to the co-localization of *RUNX*1*T*1 and *RUNX*1 signals on probably the rearranged chromosome 8 as, thus confirming the presence of the *RUNX*1/*RUNX*1*T*1 fusion gene in this translocation. FISH results revealed also the presence of a green signal on the derivative chromosome 21 and of one small orange signal (*RUNX*1*T*1) which would be probably located der(9) (**Figure 1(B)**).

4. Discussion

GS is an uncommon manifestation of AML, and the incidence of extramedullary disease in AML patients is about 3% - 8%. Isolated granulocytic sarcomas located in the pancreas are exceptional, only few cases were previously described [2] [12], and have often led to initial erroneous diagnosis. Immunohistochemical methods are essential in order to obtain correct diagnosis [13].

Although, karyotype analyses were not reported in many cases of GS in the literature, the vast majority of abnormal karyotypes in patients with AML involved t(8;21). However, the prognostic significance of the presence of GS in these patients is not clearly defined. It has been reported that AML-M2 patients with positive *RUNX*1/*RUNX*1*T*1 showed good response to the treatment, with relatively high complete remission rate and long duration of remission [14].

In this study, we report a male patient with a suspicious pancreatic GS concurrent with AML type FAB-M2. Because the general state of the patient was quickly altered, confirmation of the diagnosis by pathology and/or immunohistochemistry evaluation of the tumor was, infortunately, not possible. The karyotype revealed a novel three-way translocation t(8;9;21)(q22;p24;q22). Fluorescence *in situ* hybridization studies revealed the presence of the *RUNX*1/*RUNX*1*T*1 chimeric gene which clearly indicates that the *RUNX*1/*RUNX*1*T*1 fusion from t(8;21) is one of the main causes of leukemogenesis in the variant translocations associated with t(8;21).

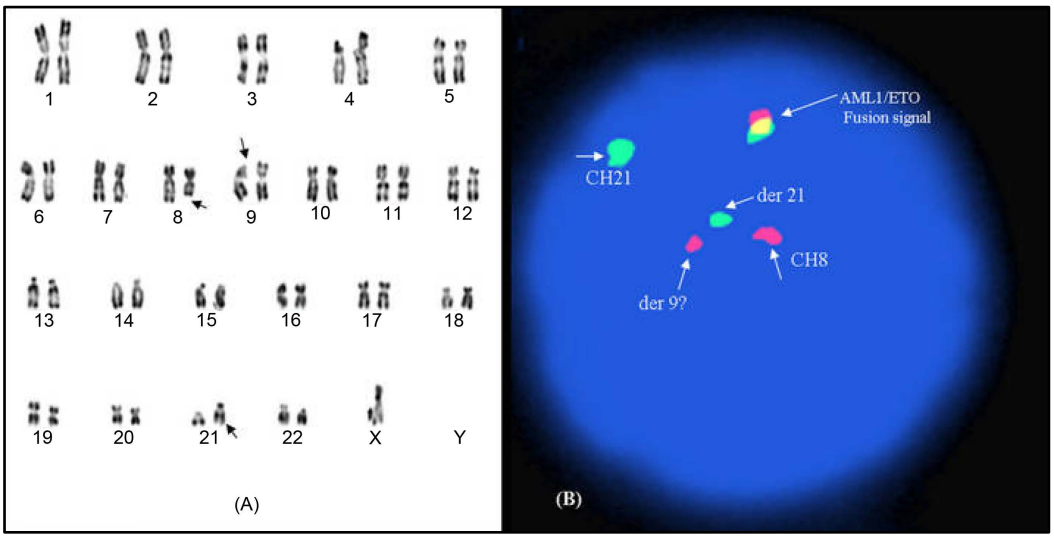

Figure 1. (A) R-banded karyotype of the BM cells showing t(8;9;21)(q22;p24;q22). Arrows indicate the aberrant chromosomes; (B) FISH using dual-color probes for *ETO* (*RUNX*1*T*1) (Orange) and *AML*1 (*RUNX*1) (green) on an interphase cell shows one fusion, two orange, and two green signals.

As far as we know, this is the first time in which we describe a variant t(8;21) in GS with AML and we report the involvement of the 9p24 in both AML and GS. The participation of the chromosome 9 in a variant t(8;21) has never been described before in GS with AML however, Kawakami *et al*. [15] recently, reported the involvement of 9q34 breakpoint in a novel variant of t(8;21) in a case with AML-M2. However, many other chromosomes were found implicated in a three-way translocation with t(8;21) as described in **Table 1** including the case we reported here.

The phenomenon is already difficult to explain. The mechanism of the occurrence of GS with t(8;21) may be related to the deregulation of Core Banding transcription factors involved in cell recognition and adhesion. The involvement of a third chromosome complicated much more the molecular pathogenetic mechanism.

Generally, chromosome 9p24 abnormalities are rare and sometimes involve *JAK*2 tyrosine kinase which is well known. The subset with *JAK*2 translocations are usually associated with myeloproliferative neoplasms and harbor a missense somatic mutation (JAK2V617F), suggesting a cause-effect relationship [31]. Functionally, the V617F mutation enhanced the *JAK*2 kinase activity, and conferred erythropoietin hypersensitivity in the affected cells [31] [32]. Many of the effects of *JAK*2 activation in the cells are mediated by the signal transducers and activators of transcription (STAT), and JAK2-STAT signaling is frequently activated both in hematologic malignancies and solid tumors [33] [34].

The prevalence of JAK2-V617F in *de novo* AML is low, around 3%. Recently, Lee *et al*. [32] and Vicenti *et al*. [35] detected this mutation in *de novo* AML with t(8;21)(q22;q22) in 16.6% (2/12) and in 21.4% (3/14) respectively.

Table 1. Participating chromosomes in complex variant translocations of t(8;21).

Translocations[a]	Third chromosome	Reference (some examples)
T(1;21;8)	1	Gmidène *et al*. [16]
T(2;8;21)	2	Zhang *et al*. [14]
T(3;8;21)	3	Giles *et al*. [17]
T(4;21;8)	4	Maseki *et al*. [18]
T(5;8;21)	5	Kikuchi *et al*. [19]
T(6;8;21)	6	Shinagawa *et al*. [20]
7q32	7	Gallego *et al*. [21]
T(8;21;8)	8	Xue *et al*. [6]
9q34	9	Kawakami *et al*. [15]
T(8;9;21)	9	Recent report
T(8;10;21)	10	Lee *et al*. [22]
11p13	11	Minamihisamatsu *et al*. [23]
T(8;12;21)	12	Farra *et al*. [24]
T(8;13;21)	13	Udayakumar *et al*. [25]
T(8;14;21)	14	Takahashi *et al*. [26]
T(8;15;21)	15	Watanabe *et al*. [27]
T(8;17;15;21)	17	Vieira *et al*. [28]
18q23	18	Gallego *et al*. [21]
19q13	19	Harrisson *et al*. [29]
T(8;20;21)	20	Wong *et al*. [30]
Complex[c]	X	Kokate *et al*. [31]

Although, the consequence of this mutation in leukemia pathogenesis remains elusive at this stage, these data could suggest, that this mutation is an additional genetic event in some patients with AML that contributes to the myeloid proliferation by diverse mechanisms [36], but has no impact on the evolution of the disease as demonstrated by Vicente *et al*. [35].

To the best of our knowledge, we report here a novel variant translocation (8;9;21)(q22; p24;q22) never described before in AML with GS and even in the isolated AML-M2.

5. Conclusion

We conclude that, the characterization of genetic aberrations in AML concurrent or not with GS has substantially improved our understanding of the pathogenesis of this disease and is of growing importance for more efficient risk assessment for individual patients. Thus, further accumulation of similar cases with variants of t(8;21) is needed.

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