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A rare case of acute myeloid leukemia with t(12;19)(q13;q13)

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ABSTRACT

Acute myeloid leukemia (AML) is characterized by chromosomal abnormalities affecting both prognosis and course of treatment. While most AML patients have well described chromosomal aberrations, around 10% present with rare chromosomal abnormalities.

We herein, report a rare balanced translocation t(12;19)(q13;q13) in a 66-year old M5-AML patient identified by Conventional cytogenetic analysis and confirmed by SNP array. We suggest that t(12;19) as a sole chromosomal abnormality could be associated with a poor prognosis. Further studies are needed to understand the molecular basis of this translocation in AML.

1. Introduction

Acute Myeloid leukemia (AML) is a heterogeneous disorder characterized by infiltration of the bone marrow, blood and other tissues by proliferating clonal myeloid progenitors or blasts. Diagnosis of AML relies on bone marrow/peripheral blood cytology and is reinforced by immunophenotypic and genetic analyses. Numerous cytogenetic abnormalities were identified in AML subtypes and have been linked to distinct clinical presentations and prognosis [1]. Cytogenetic abnormalities in AML are considered as independent prognostic factors and provide the framework for a stratified treatment approach [2]. In the 2016 World Health Organization (WHO) revised classification, acute myeloid leukemias were classified into AML with recurrent chromosomal abnormalities [3]. In the absence of well-defined translocations, or mutations such as *CEBPα* or *NMP1* (AML NOS, Not otherwise specified), a classification very similar to the FAB (French-American-British) classification system, which divides AML into 8 subgroups (M0 to M7) based on leukemic cell type and maturity, is used [4].

Around 10% of AML patients present with rare chromosomal rearrangements [2], some of which have been associated with an intermediate or adverse prognosis. Many of the described abnormalities have been well characterized and delineated at the molecular level while others remain scarcely investigated. We herein, present a case of M5-AML with a translocation t(12;19)(q13;q13) as a sole cytogenetic anomaly along with a concise review of four previously described t(12;19) cases in AML.

2. Case report

A 66-year-old Lebanese female, with a good performance status (PS 1), presented to the clinic for general weakness, night sweats and palpable right axillary lymph node. Blood tests revealed leukocytosis with white blood cells count (WBC) of 134,000/μL and 85% of blasts on peripheral smear. The patient also had moderate anemia with a hemoglobin count of 10.4 g/dl and a normal platelet count of 161,000/μL.

Biopsy of the axillary lymph node showed 80% of blast cells, consistent with acute myeloid leukemia with monoblastic component FAB M5. Bone marrow aspirate showed 70% of blast cells consisting of monoblasts (87%) and promonocytes (10%) in addition to few neutrophils. Flow cytometry revealed bone marrow infiltration with 65% of monoblasts expressing CD33, CD15, CD16, CD11b, CD11c, CD56 and MPOi.

Conventional cytogenetic workup was performed on bone marrow aspirate. Two short term unstimulated cell cultures were set up in RPMI 1640 medium supplemented with 20% FBS followed by RHG banding. Twenty-five R-banded metaphases were karyotyped and analyzed using

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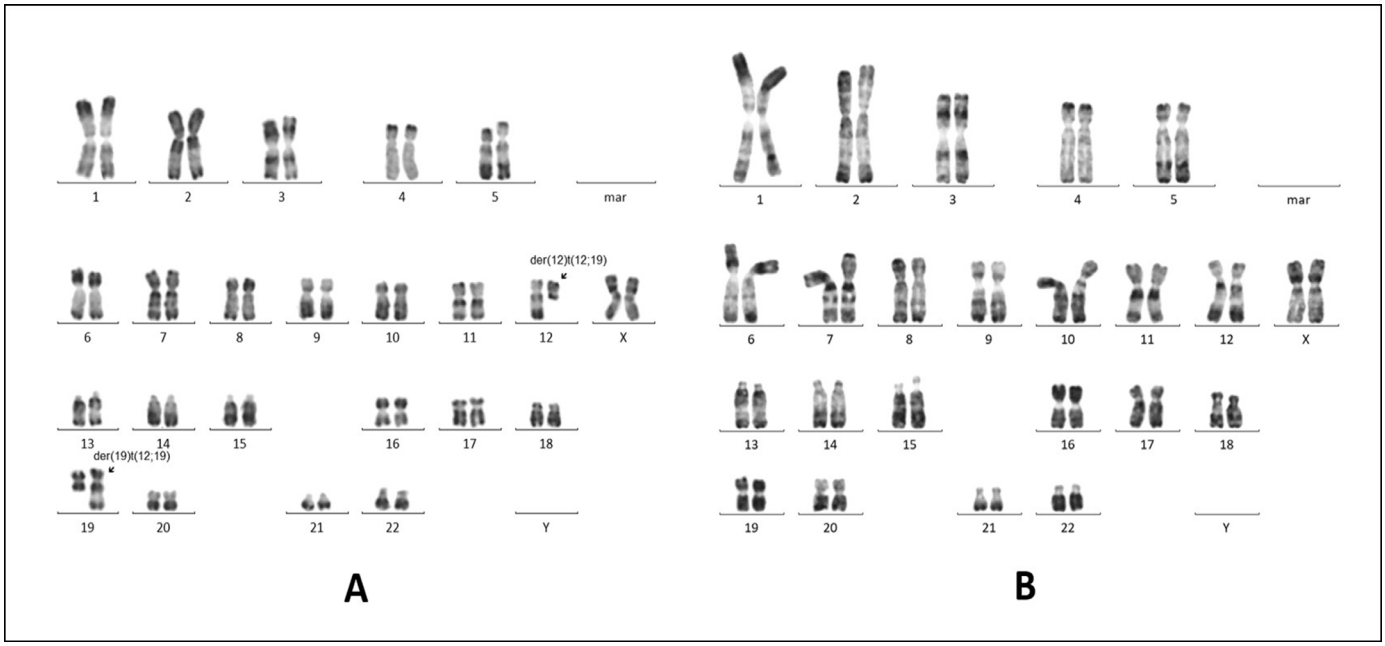

Fig. 1. (A) Unstimulated bone marrow karyotype showing t(12;19)(q13;q13), (B) Stimulated peripheral blood karyotype showing a normal female pattern 46,XX.

Ikaros software (Metasystems, Germany), according to ISCN 2016 [5]. Karyotype analysis showed the presence of an apparently balanced translocation: 46,XX,t(12;19)(q13;q13)[25] (Fig. 1A). In order to rule out a constitutional rearrangement, a stimulated peripheral blood cytogenetic analysis was performed. Blood karyotyping showed a normal female pattern in all examined cells: 46,XX[20] (Fig. 1B), confirming the acquired nature of the t(12;19) translocation.

In addition to karyotyping, molecular cytogenetic analysis using SNP array CytoScan 750K, from Affymetrix (USA) was performed in order to capture eventual losses or gains at the translocation site or further chromosomal imbalances undetected by the conventional technique. Microarray results confirmed the balanced status of the t (12;19) in this patient (Fig. 2). No additional significant gains or losses were identified.

The patient received induction chemotherapy with "7 + 3" regimen with idarubicin (12 mg/m^2 for three days) and cytarabine (150 mg/m^2 for seven days) along with prophylaxis against infections and tumor lysis syndrome, which were well tolerated. WBC fell to a nadir of 200/μL at day 9, complicated by febrile neutropenia and colitis treated with broad spectrum antibiotics. She started recovering from neutropenia at day 14 with an increase in WBC to 1,800/μL. Response to treatment was then evaluated with a bone marrow aspirate at day 21 and showed

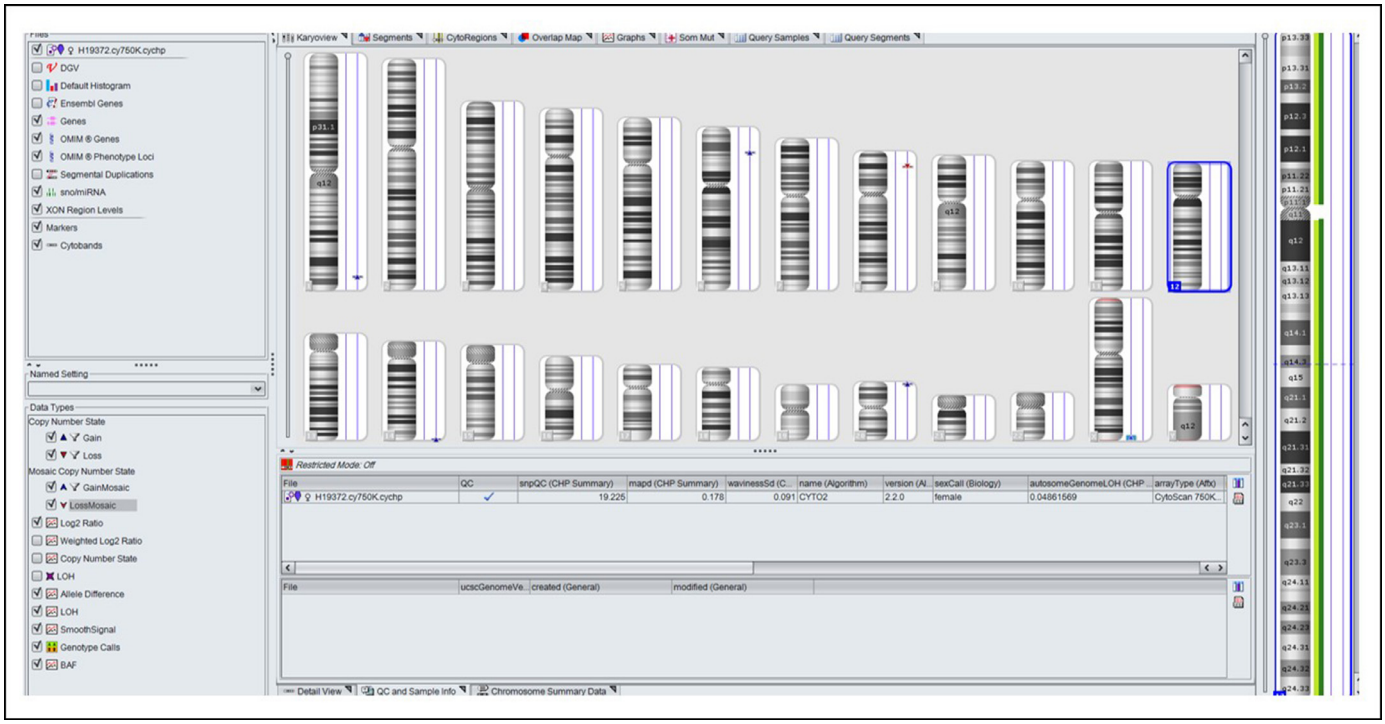

Fig. 2. SNP array result showing the presence of few benign CNVs and confirming the balanced status of the t(12;19)(q13;q13).

failure to achieve complete remission with persistence of 50% of blast cells. No cytogenetic follow up was requested on this bone marrow aspirate. Hence, she received re-induction therapy with FLAG-ida regimen (fludarabine, cytarabine, G-CSF and idarubicin), complicated with severe neutropenia, and pulmonary hemorrhage with acute respiratory distress syndrome, which caused demise of the patient after 3 months of diagnosis.

3. Discussion

In 1988, Paietta *et al.* reported for the first time a t(12;19)(q13;q13) in an AML patient [6]. Since this initial report, to our knowledge, only five cases of hematologic disorders with t(12;19) have been described in the literature. Six cases of t(12;19) have been reported in different types of solid tumors. Five cases had a t(12;19) with a complex karyotype and only one case of hemangiopericytoma presented an isolated t(12;19) with no information with respect to the prognosis. The Mitelman database for chromosomal aberration and gene fusions, Atlas of genetics and cytogenetics in oncology and haematology, and PubMed were all searched, featuring four AML cases mainly classified as FAB M1 or M2 and one case of lymphoplasmacytoid lymphoma with t(12;19)(q13;q13) [6–9]. Table 1 summarizes the clinical and cytogenetic findings in the previously published AML cases as well as the current case.

To date, the genes involved in this translocation are not well delineated. Among the four published cases of t(12;19) AML, three patients were males and one female with a median age of 50 years (range 13 – 63). Median WBC counts at diagnosis was around 3,900/μL (range 2,600 – 5,100). Two patients had M2 blasts morphology and one patient had M1 morphology. Blasts morphology was not described in the fourth patient. In all reported cases, t(12;19)(q13;q13) was identified along with other cytogenetic abnormalities. All patients were diagnosed with complex karyotypes and had adverse clinical outcomes. Three of these cases died 1 to 2 months following diagnosis; survival data was not available for the fourth patient (Table 1).

Our patient displayed an M5-AML morphology and t(12;19) as a sole chromosomal rearrangement. She had a poor clinical outcome with failure to achieve complete remission post-treatment and passed away 3 months after diagnosis. No follow up sample was available to monitor the evolution of this translocation or evaluate eventual occurrence of additional chromosomal abnormalities. A number of medical complications developed rapidly, preventing additional sampling of bone marrow aspirate for cytogenetics and further molecular analyses. Unlike previously reported t(12;19) AML cases, our patient did not present with complex chromosomal rearrangements. Complex karyotypes are found in around 10 to 12% of AML patients and are usually associated with a poor prognosis [2,10]. All AML cases with t(12;19) reported so far had associated complex chromosomal abnormalities, it has therefore not been clearly determined which of the complex karyotype or the t(12;19) were responsible for the adverse prognosis. Our case outlines a potential independent prognostic factor for t(12;19) in AML patients regardless of other associated chromosomal abnormalities.

In conclusion, we report for the first time t(12;19)(q13;q13) as a sole acquired abnormality in an M5-AML patient. The data we present here suggest that t(12;19) might be linked to a poor prognosis whether identified in the context of a complex karyotype or as a sole abnormality. Additional reported cases would be helpful for a better assessment of t(12;19) (q13;q13) prognostic value. Furthermore, molecular studies for the identification of a potential gene fusion or deregulation could contribute in establishing the role and impact of t(12;19)(q13;q13) in the pathogenesis and development of AML.

Informed consent

The patient signed an informed consent.

Table 1
Reported cases of AML with t(12;19)(q13;q13).

Reference	Age	Sex	Diagnosis (FAB)	Treatment	Survival after diagnosis (months)	Karyotype
Paietta *et al.* 1988 (6)	61	F	M2	Daunorubicin/ Arabinoside	2	46~48,XX,+8,-13,-17,+18, t(12;19)(q13;q13.3),t(5;17)(q12;q12),+1~3mar
Paietta *et al.* 1988 (6)	63	M	M1	Low-dose Cytosine arabinoside	1	46,XY,-3,t(12;19)(q13;q13.3),+mar
Paietta *et al.* 1988 (6)	63	M	M2	High-dose Cytosine arabinoside /Amsacrine	2	41,X,Y,-3,-5,-7,17p+,-18,-22,t(12;19)(q13;q13.3),+mar
						42,X,-Y,-3,-5,-7,-18,-22,t(12;19)(q13;q13.3),+mar,+mar
						46,XY
Scheurlen WG *et al.* 1999 (7)	13	M	NA	NA	NA	46,XY,t(10;11)(p13;q13),t(12;19)(q13;q13),i(17)(q10),der17,+mar
Our patient	66	F	M5	Idarubicin/ Cytarabine FLAG-ida	3	46,XX,t(12;19)(q13;q13)

F: female; M: male; NA: not available

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Declaration of Competing Interest

The authors declare no potential conflicts of interest.

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