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Agressive Acute Myeloid Leukemia with inv(3)(q21q26.2): A Case Report

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Abstract

Acute myeloid leukemia with inv(3)(q21q26.2) is an aggressive and relatively rare subtype of leukemia. Typically, it may present de novo or arise from a prior myelodysplastic syndrome; therefore, multilineage dysplasia can be a common finding. This report describes the case of a 38-year-old woman, who presented a clinical indication of acute leukosis. Blood tests results showed LDH 708 U/L, PCR 230 mg/L, hemoglobin 7.5 g/dL and WBC count of 92.45 x 10^9/L in peripheral blood (PB), 25% of blasts, 48% of vacuolated monocytes with irregular nuclei, dysplastic granulocytes, and giant hypogranular platelets. The immunophenotyping of PB sample showed the presence of 11.5% of myeloid blasts and 81.4% of cells with characteristics and maturation pattern of monocytic lineage; some of them exhibited phenotypic alteration. Karyotype analysis of the PB sample showed [inv(3)(q21q26)] with a secondary abnormality [t(1;15)(q10;q10)]. Pleural fluid analysis showed LDH 748 U/L and 2.950 cells/mm^3 of which 54% had increased size and immaturity features. Due to the aggressiveness of the disease and secondary clinical events, the patient died four days after being hospitalized. This case demonstrated the importance of detailed laboratory tests correlations in achieving differential diagnosis of hematologic malignancies. The initial diagnosis of AML with monocytic differentiation was suspected after analysis of immunophenotyping which presented a large monocytic component. However, the occurrence of inv(3)(q21q26), associated with multilineage dysplasia, pointed to AML with inv(3)(q21q26). The severity of the disease was demonstrated by the presence of malignant cells in pleural fluid, which represents information not frequently reported in other studies.

Keywords: *Acute myeloid leukemia; AML with inv(3); cytogenetic analysis.*

Introdution

Acute myeloid leukemia (AML) with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); (RPN1-EVI1) is a relatively rare subtype of leukemia that may present de novo or secondary to myelodysplastic syndrome (MDS). This entity was included in the 4th edition of the World Health Organization (WHO) classification of Tumours of Hematopoietic and Lymphoid Tissues as an AML with recurrent cytogenetic abnormalities [1]. This genetic abnormality involves the ecotropic viral integration site-1 (EVI1) oncogene at 3q26.2 and ribophorin1 (RPN1) gene at 3q21, leading to the RPN1–EVI1 fusion transcript. This rearrangement results in enhancer of EVI1 expression, resulting in increased cell proliferation, impaired cell differentiation, and inducing haematopoietic cell transformation [2].

AML with inv(3)/t(3;3) account for 1–2% of all acute myeloid leukemias [3] and it is characterized by a specially aggressive clinical behavior and poor prognosis [4]. Affected patients can present with de novo disease or secondary disease as a result of progression from an underlying MDS. Typically, patients present normal or elevated platelet counts, atypical bone marrow megakaryocytes and multilineage dysplasia [5]. In addition, myelomonocytic differentiation is common [6]. As the diagnosis of AML with inv(3)(q21q26.2) is rare, the purpose of this work was to present a case study about this leukemia subtype.

Case Report

This report describes the case of a 38-year-old woman, who presented a clinical indication of acute leukosis. The biochemical exams showed LDH 708 U/L, PCR 230 mg/L, creatinine 0.8 mg/dL and uric acid 5.5 mg/dL. The peripheral blood (PB) analysis presented a total WBC count of 92.45 x 10^9/L, hemoglobin 7.5 g/dL, 4 erythroblasts and platelet count of 269 x 10^9/L. Morphological analysis was proceeded with MayGrumwald Giemsa-stained in PB smears and demonstrate 25% of blasts presenting a high nuclear/cytoplasm ratio, reticular chromatin and visible nucleoli; presence of 22% of granulocytes that had delayed maturation and some dysplastic characteristics such as hypogranular granulocytes and hypersegmented nucleus; 48% of vacuolated monocytes with irregular nuclei; and giant and hypogranular platelets (Figure 1).

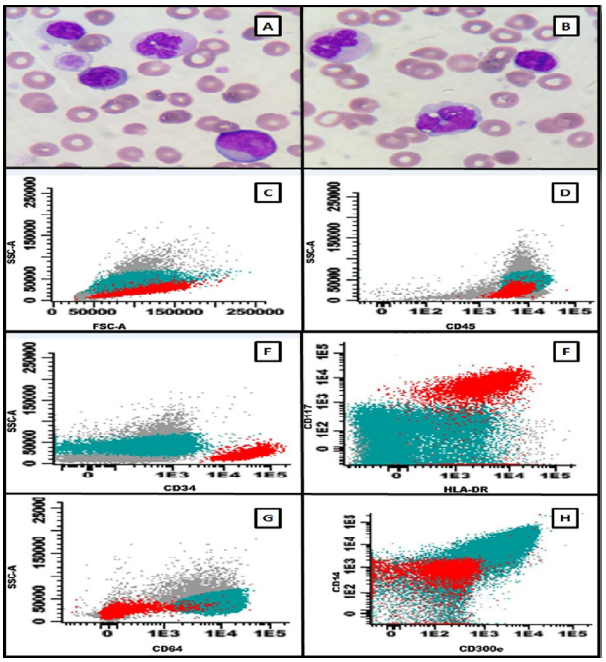

Figure 1. *Presence of blasts and dysplastic features were observed in blood smear, and Immunophenotypic profiles of blast and monocytic cells in peripheral blood sample by eight-color flow cytometry. Blast cells are painted in red and monocytic cells in green. A) Peripheral blasts, hypogranular and hypersegmented neutrophils, and giant and hypogranular platelets; B) vacuolated monocytes with nuclear alterations, and hypogranular and hypersegmented neutrophils; C) Side and forward scatter properties, D) CD45 expression in blasts and monocytic cells, E) CD34 expression in blast cells, F) blasts positive for CD117 and HLA-DR, G) Monocytic cells CD64+, and H) shows the maturation of monocyte series.*

The immunophenotyping of PB showed the presence of 11.5% of myeloid blasts (CD34++, CD45+, CD13+, CD117+, HLA-DR+, CD33+) and 81.4% of cells with characteristics of the monocytic lineage (CD64+) which include promonocytes and monoblasts. Some of them exhibited phenotype alteration, such as HLA-DR expression. The majority of monocytic cells were mature monocytes (70%) following immature cells (promonocytes and monoblast, 30%). Thus, 35.1% of total cellularity was immature cells, composed by myeloid blasts, monoblasts and promonocytes (Figure 1). Furthermore, granulocytic series presented dysplastic alterations such as hypogranularity low side scatter (SSC).

Cytogenetic analysis of PB showed a chromosome inversion [inv(3)(q21q26)] with a secondary karyotypic abnormality [t(1;15)(q10;q10)] (Figure 2). FLT3 mutation analysis was performed using DNA isolated from PB samples. A PCR assay was used to detect DIT and D835 point mutations of the FLT3 gene, however it was not found.

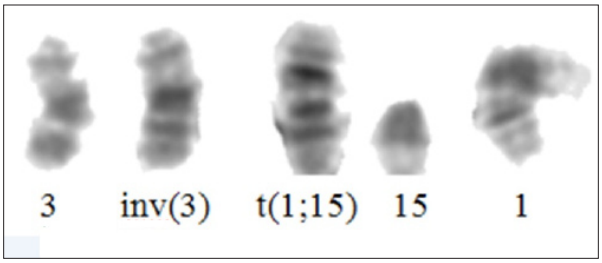

Figure 2. *Chromosome rearrangements and normal chromosome (to compare) from the studied patient.*

Pleural fluid sample analysis was also performed and showed LDH 748 U/L, and 2.950 cells/mm3 of which 54% showed increased size and immaturity features. Regarding that, the patient died four days after entering the hospital.

Discussion

The present report further elucidates the laboratory features of a patient with AML with inv(3)(q21q26). AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2) is an aggressive disease associated with poor response and high rates of resistance to conventional chemotherapy, short survival (approximately 10 months) and poor prognosis [7]. Overall survival at one year was barely 33%, which further decreased to 3% at 5 years. This poor outcome was not affected by age, PB count at diagnosis, BM blast count, or the presence of additional cytogenetic abnormalities [6]. In this case, the patient died four days after being admitted in the hospital; the

severity of the disease could be demonstrated by the presence of malignant cells in pleural fluid, which was never reported in other studies known so far.

According to the WHO (2008) criteria to AML diagnosis includes morphological, immunological, cytogenetic, genetic, and clinical features. This case study is relevant to demonstrate the importance of a detailed correlation of laboratory exams to the WHO classification to AML [1]. Through the analysis of immunophenotyping by flow cytometry, the initial suspect diagnosis was of AML with monocytic differentiation, due to the presence of a large monocytic component. AML of monocytic lineage are characterized by the presence of more than 80% of cells from the monocytic lineage, including monoblasts, promonocytes and monocytes, and less than 20% from the granulocytic 3 inv(3) t(1;15) 15 1 cells [1]. The final diagnosis should be performed after bone marrow (BM) analysis. In this case, however, the BM sample collection was not performed because the patient died a few days after being admitted to the hospital. Therefore, the observation of a chromosome inversion [inv(3)(q21q26)] by cytogenetic defined the diagnosis as AML with inv(3)(q21q26).

This case study demonstrates the importance of a detailed correlation of laboratory tests. AML with inv(3)/t(3;3) is a primarily disease of adults; and the median age is approximately 50 years old (27 to 77 years old) [6, 7]. In our case, the patient was 38 years old. In general, the patients present anaemia and normal to elevated platelet count. PB changes include dysplasia that can be apparent in neutrophils, causing alterations in nuclear lobulation, cytoplasmic granulation and presence of blasts. Giant and hypogranular platelets are common [5]. These laboratorial characteristics were observed in this case. A subset of cases has less than 20% blast cells at the time of diagnosis [8]. It has been shown that dysplasia was present in BM in more than 90% of cases [6]. However, this result is related to BM samples, and in this case, it was found aproximately 20% of blast cells in PB. The predominant immunophenotype characterized by expression of the pan-myeloid antigens CD33, CD13, CD117 as well as the immature markers CD34, CD38 and HLA-DR were noted in >80% of patients; megakaryocytic markers (CD61) are extremely uncommon (<10%) [7, 9]. In this case, by flow cytometry, the presence of blast cells that express CD13, CD33, HLA-DR, CD34 and CD38 was proven.

Unlike some other types of AML recurrent genetic abnormalities, additional cytogenetic abnormalities are common in AML associated with inv(3)/t(3;3). The most common additional abnormality in this series was monosomy 7, followed by a complex karyotype in approximately one-third of the cases [6]. In the reported case, it was observed a secondary karyotypic abnormality [t(1;15)(q10;q10)]. A low incidence of the FLT3 mutation by internal tandem duplication was already observed [6] and indicate that mutation is uncommon in this type of AML.

AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2) is an aggressive disease associated with poor response and high rates of resistance to conventional chemotherapy, short survival (approximately 10 months) and poor prognosis [7]. Overall survival at 1 year was barely 33%, which further decreased to 3% at 5 years. This poor outcome was not affected by age, peripheral blood count at diagnosis, bone marrow blast count, or the presence of additional cytogenetic abnormalities [6]. In this case, the patient died four days after entering in the hospital and the severity of the disease could be demonstrated by the presence of malignant cells in pleural fluid. In conclusion, this case demonstrated the importance of using several laboratory exams to assist in achieving a differential diagnosis of hematologic malignancies.

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