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SHORT COMMUNICATION

Acute promyelocytic leukemia associated with the PLZF-RARA fusion gene: two additional cases with clinical and laboratorial peculiar presentations

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Abstract Acute promyelocytic leukemia (APL) is characterized by the presence of the t(15;17) and PML-RARa rearrangement, with good response to treatment with retinoids. However, few cases of variant APL involving alternative chromosomal aberrations have been reported, including t(11;17)(q23;q21) (Wells et al. in Nat Genet 17:109–113, 1; Arnould et al. in Hum Mol Genet 8:1741–1749, 2) t(5;17)(q35;q12-21), t(11;17)(q13;q21) (Grimwade et al in Blood 96:1297–1308, 3) and der(17) (Rego et al. in Blood (ASH Annual Meeting Abstracts)114:Abstract 6, 4), whereby RARa is fused to the PLZF, NPM, NuMA, and STAT5b genes, respectively, have been described. These cases are characterized by distinct morphology, clinical presentation, and in respect to PLZF, a lack of differentiation response to retinoids leading to the need of different approaches concerning diagnostic methods and therapeutics. This paper describes two cases of APL associated with the PLZF-RARA fusion gene enrolled in the IC-APL trial that is a non-randomized, multicenter study conducted in Brazil, Mexico, Chile and Uruguay with the aim to improve the treatment outcome of APL patients in developing countries. These cases, although rare, offer a challenge to its early recognition and proper conduction.

Keywords Acute promyelocytic leukemia · PLZF-RARA · t(11;17) · Molecular rearrangement · Promyelocytic variant translocation

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Introduction

In the vast majority of patients with acute promyelocytic leukemia (APL), the t(15;17) is detected. It leads to the generation of the PML-RARa fusion gene, which predicts favorable response to retinoids. However, a sizeable minority of APL cases lack the classic t(15;17). Variant chromosomal aberrations have been reported, including t(11;17)(q23;q21), t(5;17)(q35;q12-21), t(11;17)(q13;q21) [1], and der(17) [2], whereby *RAR*a is fused to the *PLZF*, *NPM*, *NuMA*, and *STAT5b* genes, respectively. In common with *PML-RAR*a-associated APL, patients with fusion genes involving *NPM* and *NuMA* appear to be sensitive to ATRA [1], while those with *PLZF-RAR*a rearrangement lack of a differentiation response to retinoids, and unfavorable prognosis [3].

The IC-APL trial is a non-randomized, multicenter study conducted in Brazil, Mexico, Chile and Uruguay with the aim to improve the treatment outcome of APL patients in developing countries by establishing a clinical network that provides the conditions for the exchange of experiences among hematologists, educational activities, and expedite diagnosis. The treatment is based on the best standard of care and relies on ATRA and anthracyclines for induction and consolidation, followed by maintenance with methotrexate, mercaptopurine, and 15-day courses of ATRA given every 3 months. The detailed protocol is

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described elsewhere [4]. From June 2006 through September 2010, 215 patients with morphological suspicion of APL were evaluated, of which 183 cases harbored the t(15;17)/PML-RARA rearrangement, and two patients presented variant chromosomal aberrations here described. In the remaining 30 patients, the diagnosis of APL was discarded.

Case 1

A 38-year-female patient complained on July 2009, of dyspnea, chest pain, and fever. Blood tests revealed: Hb 12.6 g/dL, Ht 37.6%, VCM 87.5 fL, HCM 29.7 pg, WBC 23,600/μL (19.8% blasts), Platelets 43,000/μL with 86% of blasts with low nuclear-cytoplasmic ratio, medium sized with cytoplasmic granules and Auer rods, INR 1.23 (1–1.20), DHL 1583U/L (140–271), and Fibrinogen 664 mg/dL (200–400). Bone marrow aspiration showed 72% blasts with the same characteristics (Fig. 1). Immunophenotyping showed positivity to: CD13 heterogeneous, CD33 homogeneous, CD117, CD34 partial, CD4, CD65, CD11c, CD56 partial, and negativity for CD2 and HLA-DR. PML-RARa was negative. Marrow karyotype, though presenting only two metaphases, showed 46,XX,t(11,17)(q23;q22) [2]. PLZF-RARA rearrangement was detected by Southern blot. She received all-*trans* retinoic acid (ATRA) plus conventional chemotherapy with daunorubicin (45 mg/m^2) and cytarabine (3 + 7). Thirty days afterward, no remission was achieved and marrow aspiration showed 57.6% of blasts. Reinduction with mitoxantrone, etoposide, and cytarabine was started on September 2009, and after recovery, marrow aspiration still revealed 62% of blasts. She was scheduled to a third cycle of chemotherapy but died due to sepsis with active disease.

Case 2

A 48-year-male patient presented weight loss (20 kg), fatigue, and five episodes of tonsillitis for 3 months prior to hospital admission on November, 2010. Blood tests revealed: Hb 7.2 g/dL, Ht 21.4%, MCV 98.2fL, WBC 71.6 × 10^9/μL with 90% of blasts, medium to large size, abundant cytoplasm, loose chromatin, no nucleolus, with granules and Auer rods, Platelets 41 × 10^9/μL, and Fibrinogen 675 mg/dL. Bone marrow aspiration was hypercellular 86.4% myeloid blasts (Fig. 2). Immunophenotyping from bone marrow blasts revealed positivity to: CD33, CD117, CD13, CD11c, and CD11b and negativity for CD23, CD7, CD15, CD36, CD65, CD10, CD56, CD41, CD2, CD19, and HLA-DR. Karyotype showed no metaphases. PCR was positive to PLZF-RARa. The patient was scheduled to daunorubicin (60 mg/m^2) and ATRA, but no remission was achieved. Reinduction with daunorubicin (60 mg/m^2) and cytarabine (3 + 7) was started, partial remission was achieved, and while waiting for the marrow donor search, he received HIDAC and arsenic trioxide. Allogeneic hematopoietic stem-cell transplantation is scheduled.

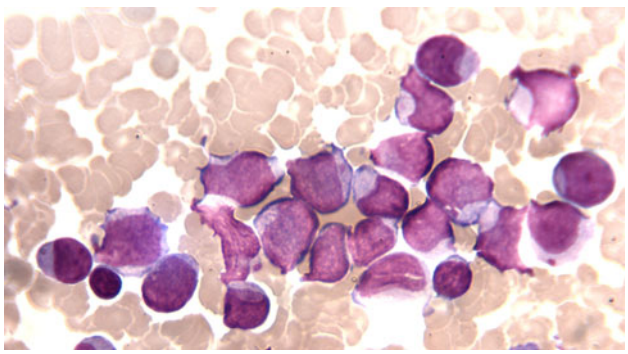

Fig. 1 Case 1 peripheral blood blast cells

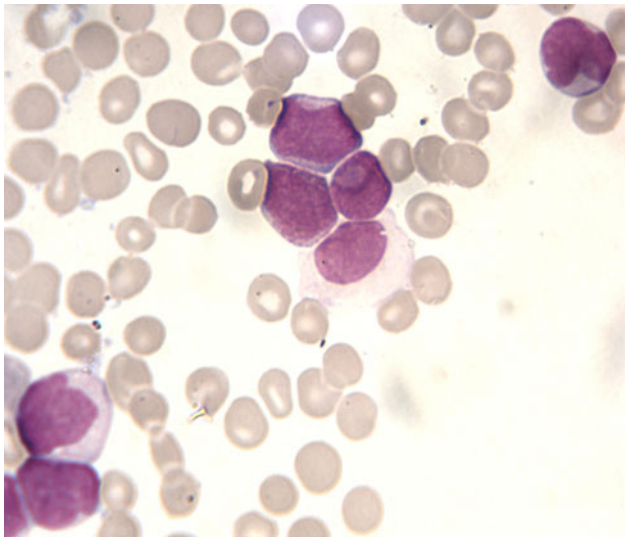

Fig. 2 Case 2 peripheral blood blast cells

Discussion

APL with PML-RARa rearrangement is described as occurring in around 20–26.4% of AMLs in Brazil [5–7]. The variant forms involving PLZF at 11q23, NUMA1 at 11q13, NPM1 at 5q35, and STAT5B at 17q11.2 are rare, and the two cases of PLZF-RARa here shown stands for a frequency of 1.08% of the 185 cases enrolled in the IC-APL, a frequency a little higher than the 0.8% described in the worldwide literature [5]. To date, none of previous Latin America studies estimated the frequency of APL variants including t(11;17).

PLZF-RARa has been reported to have atypical APL morphology in comparison to the classical PML-RARa, like regular nuclei and hypo- or microgranular cells, abundant cytoplasm, more condensed chromatin pattern in blasts, absence of Auer rods, and increased number of Pelgeroid neutrophils [8]. The cases here described, although variant, did not show an atypical morphology since they presented with granules and Auer rods.

Regarding clinical aspects, there is a tendency to hyperleukocytosis and hemorrhagic events such as DIC in the variant group. Both cases presented more than 23,000 white blood cells per μL, but none of them contemplated bleeding or low fibrinogen.

From therapeutical point of view, usually t(11;17) strongly blocks differentiation, so the PLZF-RARa variant is characterized by poor response to retinoids as a single agent and also to arsenic trioxide [9]. However, a number of studies suggest that this subset of APL is not completely resistant to differentiation approaches and may be ATRA responsive since some differentiation response to ATRA was observed, and complete differentiation was obtained when cytokines or cytostatics were used in addition to RA [10]. Despite the peculiar clinical and laboratorial presentation, there was a suspicion of promyelocytic leukemia, and patients have been treated following standardized protocols of the IC-APL, but none of them achieved remission.

Different from APL PML-RARa associated disease, it seems reasonable to consider allogeneic HSCT in first CR if a suitable donor is available in cases with t(11;17) and that is the planning for the patient of the case 2 since a compatible donor was found. Moreover, in a broader sense APL t(11;17) patients to whom allo-HSCT is not feasible, experimental approaches could be tried, but remain to be determined.

This report shows that the APL variant form, although rare, offers a challenge to its early recognition what can be achieved with the combination of careful morphology analyses, clinical presentation, and genetics tests.

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