

Myeloid natural killer cell leukemia resembling a variant of acute promyelocytic leukemia

We report a new case of myeloid/natural killer cell acute leukemia (myeloid/NK). Blast morphology and immunophenotype were similar to a variant of promyelocytic leukemia, resistant to ATRA (acute promyelocytic leukemia with zinc finger-RAR α fusion). The karyotype was normal and cells did not present RAR- α rearrangement. Genetic studies are essential for diagnosis.

A 70-year old woman was admitted to hospital with diffuse bone pain, fever for the previous 4 days and cutaneous purpura. Laboratory values were: WBC $187 \times 10^9/L$ (98 % blasts with high nuclear-cytoplasm ratio; kidney-shaped nucleus, 1-3 nucleoli and fine granular cytoplasm, 1% neutrophils and 1% lymphocytes). The hemoglobin concentration was 13.4 g/dL and the platelet count $31 \times 10^9/L$. APTT was: 33.5" (34"), INR 1.3, fibrinogen 158 mg/mL, D-dimer: 2,000-4,000 ng/mL (N< 200). Biochemical determinations were normal, except for LDH which was 760 mg/dL. Chest X-rays and an echocardiogram were normal. Bone marrow aspirate was hypercellular, 95% cells were blasts with bilobulated nucleus and fine granules resembling a microgranular variant of acute promyelocytic leukemia (APL.v) (Figure 1). Cytochemical reaction was moderate-weak with myeloperoxidase (MPO) and Sudan black-B (SBB) and negative with α -naphthol-acetate esterase stain. The immunophenotype of the blast population was: CD33⁺, CD13⁺, DR⁻, CD34⁻, CD45⁺, CD11a⁺, CD15⁺ and aberrant CD56⁺ expression (Figure 2). Samples for cytogenetic and molecular biology studies were obtained and with the provisional diagnosis of APL.v, the patient started treatment with all-trans retinoic acid (ATRA) and idarubicin (PETHEMA LAP-96 Protocol)¹

Conventional cytogenetics (included study from chromosome 11) and reverse transcriptase polymerase chain reaction (RT-PCR) assay (PML-RAR α and PLZF-RAR α) were normal. The patient was identified as having a myeloid/natural killer cell acute leukemia and treated with idarubicin and cytosine arabinoside (PETHEMA LAM-99 for patients over 65 years old). She do not respond to two cycles of chemotherapy and died.

Myeloid/natural killer cell acute leukemia is a particular form of leukemia with cytologic features similar to microgranular acute promyelocytic variant.^{2,3} Previously reported cases were distinguished by their lack of expression of HLA-DR and co-expression of myeloid and natural killer cell antigens.² Some patients may have abnormalities evolving from chromosome 17 or 11 but lack the t(15,17) and do not respond to ATRA; nevertheless by morphology and immunophenotype, these cases may be classified as acute promyelocytic leukemia (M3v).²

Acute promyelocytic leukemia is characterized by a mutation that affects the retinoic acid receptor α (RAR α).³⁻⁵ In most cases a t(15;17) (q21;q22) occurs, fusing the RAR α and promyelocytic leukemia genes resulting in a PML-RAR α chimeric protein with maturational block.⁵ This alteration may be reversed by the treatment with all-trans retinoic acid.^{6,7} APL present variant chromosomal aberrations fusing RAR α with other genes.^{8,9} The most common variant is a fusion of RAR α with the promyelocyte leukemia zinc finger (PLZF) gene.¹⁰ In this variant of APL blast cells express an aberrant CD56 marker and may present t(11,17), the variant is more often seen in old patients, is refractory to ATRA treatment³⁻⁵ and has a poor prognosis.^{2,4,5} Preliminary reports indicate that these patients may respond to a combination of ATRA and GSF or to a combination of ATRA and trichostatin (an inhibitor of deacetylase activity).

In our patient cutaneous purpura and hemostatic alterations were present at diagnosis; cytology and immunophenotype resembled the APL hypogranular variant, with CD56 expression in

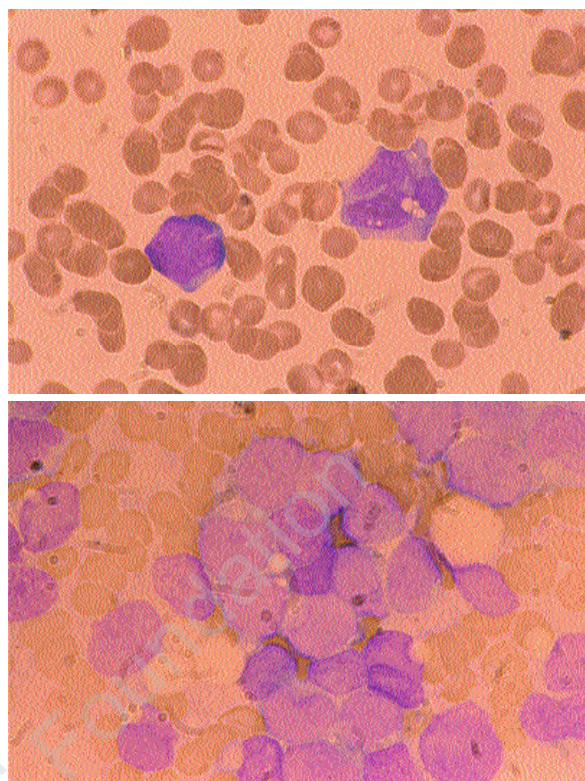


Figure 1. (A) Wright-stained myeloid/NK blasts in peripheral blood. (B) Wright-stained myeloid/NK blasts in bone marrow aspiration. Original magnification $\times 40$.

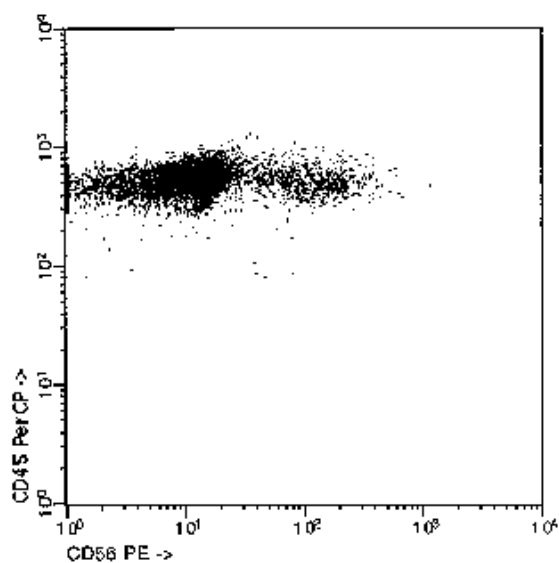


Figure 2. Flow cytometric analysis of myeloid/NK blasts, co-expression of CD45 (Y-axis) and CD56-PE (X-axis).

blast cells, and the disease was resistant to ATRA. Hemostatic disorders have been described in patients with myeloid/NK leukemia although, as in our patient, are less significant than in APL.

Myeloid/NK acute leukemia response to treatment is similar to that expected in patients with the AML treated with protocol daunorubicin and cytosine arabinoside (3 and 7 days, respectively), with a median survival of 30 months.² However 15% of these patients have a more aggressive progression and fail to respond to conventional induction treatment, similarly to the present case.

Patients with AML with morphologic features resembling M3 and M3v, should be analyzed by flow cytometer. The panel of monoclonal antibodies may include: HLA-DR, CD34, CD33, CD13, CD15, CD16, CD56 and CD11a antigens. Complete cytogenetic and RT-PCR assays for PML-RAR α and PMLZ-RAR α are also needed to confirm the diagnosis in these patients.

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