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Short Report

# HLA-DR antigen-positive acute promyelocytic leukemia

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ABSTRACT

Acute promyelocytic leukemia (APL) with t(15;17)(q22;q21)/PML-RARα is a subtype of acute myeloid leukemia (AML) with distinct morphologic and immunophenotypic characteristics. It is a highly aggressive disease that requires rapid diagnosis and early intervention. In addition to morphologic evaluation, flow cytometry has been widely used to facilitate prompt diagnosis of this disease. Compared with other types of AML, APL typically displays a triad of absent or weak CD34, absent HLA-DR, and positive CD117. HLA-DR positive APL is extremely rare and its clinical and pathological features have not been reported. A total of 45 cases of APL with t(15,17)/PML-RARα were diagnosed at Harbor-UCLA Medical Center from year 2006 to 2015. Among them, only two cases were positive for HLA-DR by flow cytometry immunophenotyping. Here we describe the clinical, morphologic, immunophenotypic, and cytogenetic features of these two cases.

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## 1. Introduction

Acute promyelocytic leukemia (APL) with t(15;17)(q22;q21)/PML-RARα is an aggressive subtype of acute myeloid leukemia (AML). Affected patients are at significant risk to develop life-threatening coagulopathy if left untreated. However, outcomes in APL patients have dramatically improved by prompt diagnosis and early initiation of specific treatment including ALL-trans-retinoic acid (ATRA) and arsenic trioxide. Therefore, APL is considered a medical emergency and the ability to quickly establish the diagnosis before the disease progresses to irreversible is crucial for successful patient management. The t(15;17)(q22;q21) PML/RARα defines the disease and serves as the molecular basis of the treatment with ATRA.

Diagnosis of APL traditionally relies on the morphologic evaluation of the leukemic cells followed by confirmation by cytogenetic or molecular detection of the t(15;17)(q22;q21) PML/RARα by karyotyping, fluorescence in situ hybridization (FISH), or reverse transcriptase-polymerase chain reaction (RT-PCR). The confirmatory cytogenetic and molecular studies are relatively time-consuming, especially in many community practice settings. According to the National Comprehensive Cancer Network (NCCN) Guidelines, ATRA should be started before genetic confirmation in patients with clinical and pathological features of APL because early initiation of ATRA may prevent the lethal complication of bleeding resulting from disseminated intravascular coagulation (DIC). Unfortunately, a definitive morphologic diagnosis is not always possible, particularly when dealing with morphologic variants.

To facilitate rapid diagnosis of APL, flow cytometry has been widely used and extensively studied. Compared with other types of AML, the most consistent immunophenotype in APL includes absent or weak CD34, absent HLA-DR, and positive CD117. Other flow cytometric features described in the literature that are commonly seen in APL include heterogeneity of high side scatter, absent, low-level, or less frequent expression of CD10, CD11a, CD11b, CD11c, CD18, CD45RO, CD105, and CD133 (Dong et al., 2011). Only rare HLA-DR positive APL cases were reported, and in these reports, the clinical and pathological features were not described.

In this article, we report the clinical, morphologic, immunophenotypic, and cytogenetic features of two cases of HLA-DR positive APL.

## 2. Patients and methods

A retrospective review identified 45 APL with t(15;17)(q22;q21)/PML-RARα cases diagnosed at Harbor-UCLA Medical Center (Torrance, CA) between year 2006 and year 2015. The t(15;17)(q22;q21)/PML-RARα was confirmed by karyotyping, FISH, and/or RT-PCR studies performed at Quest Diagnostics Nichols Institute (San Juan Capistrano, CA). Among them, 2 cases carried a HLA-DR (+) immunophenotype by flow cytometry.

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Clinical data and pathologic specimens were reviewed. The clinical information of the 2 patients with HLA-DR positive APL including age, sex, presenting symptoms, laboratory testing, imaging, therapeutic regimens, followup, and survival were obtained through the computerized data base searching. Immunophenotypic features were determined by flow cytometric analysis. Positivity was defined as staining of 20% or more of leukemic cells.

## 3. Case reports

### 3.1. Case A

A 20-year-old female with no significant past medical history who initially presented to her primary physician with sudden onset of fever, dizziness, weakness, menorrhagia, gum bleeding, and bruising was found to have marked anemia (Hgb 6.8 g/dL), mild leukopenia (WBC 3 K/mm$^3$) and marked thrombocytopenia (platelet 30 K/mm$^3$) at an outside hospital. She received transfusions (2 units of packed RBC and 1 unit of apheresis platelets), was given acetaminophen, and was transferred to Harbor-UCLA Medical Center (HUMC) for further workup. She denied trauma, neck/chest/pelvic pain, headache, abnormal vaginal bleeding, sexual activity, nausea, vomiting, dysuria, shortness of breath, or upper respiratory symptoms. At her presentation at HUMC, she was afebrile, and her vital signs were reassuring. The general physical examination revealed scattered ecchymotic lesions, but otherwise was unremarkable with no palpable cervical, axillary, or inguinal lymphoadenopathy. A CBC count revealed a white blood cell count of 5.2 K/mm$^3$ (reference range 4.0–10.0 K/mm$^3$), a hemoglobin concentration of 9.7 g/dL (reference range 11.9–14.9 g/dL), and a platelet count of 39 K/mm$^3$ (reference range 150–420 K/mm$^3$). Review of the peripheral blood smear showed many blasts with the following 100-cell differential: segmented neutrophils 6, bands 2, metamyelocyte 1, myelocyte 1, promyelocytes 2, blasts 55, and lymphocytes 33. The blasts were variable in size from small to large, had round to oval to irregular nuclei, fine chromatin, some containing distinct/prominent nucleoli, and small amounts of basophilic cytoplasm sometimes with azurophilic granules (Fig. 1A–C). Bilobed nuclei were seen in occasional blasts. Rare blasts contained a thin Auer rod. Faggot cells were not found. The findings were consistent with acute myeloid leukemia. Additional laboratory studies at presentation included normal blood chemistry tests except for a mild decrease in potassium level at 3.5 mmol/L (reference range 3.6–5.1 mmol/L) and a mild decreased in calcium level at 8.7 mg/dL (reference range 8.9–10.3 mg/dL). Liver function tests were normal. The serum lactate dehydrogenase level was 189 U/L (reference range 98–192 U/L). Coagulation studies showed a prothrombin time (PT) of 16.1 s (reference range 11.8–14.7 s), a partial thromboplastin time (PTT) of 32.5 s (reference range 24.1–33.6 s), and a decreased fibrinogen level of 175 mg/dL (reference range 204–485 mg/dL). D-dimer was markedly elevated to 9000 ng/mL DDU (reference range 0–250 ng/mL DDU). Urine analysis revealed the following: protein 4+, glucose 1+, bilirubin 1+, blood 3+, WBC 16/HPF (reference range 0–3), RBC > 182/HPF (reference range 0–2), bacteria 1+/HPF. Human immunodeficiency (HIV) 1 DNA PCR was negative. Chest X-ray and computed tomography (CT) scan of the abdomen and pelvis were unremarkable except for a 3.0 cm right ovarian cyst. The patient was admitted and a bone marrow aspiration and biopsy was performed. The smears of bone marrow aspirate (Fig. 2) were aparticulate but contained numerous blasts morphologically similar to those seen in the peripheral blood. A few abnormal promyelocytes and rare hypogranulated neutrophils were also found. However, faggot cells were not identified. Flow cytometry immunophenotyping of the blast population (Fig. 3) showed the blasts expressed CD13, CD33, CD34 (partial), CD38, CD117, HLA-DR, and cytoplasmic myeloperoxidase (MPO), without co-expression of T- and B-cell markers, CD14, CD41, CD56, CD61, or TdT. MPO cytochemical stains performed on the bone marrow aspirate smear showed subset of blasts were positive with variable intensities. The bone marrow trephine biopsy sections showed markedly hypercellular (>95%) bone marrow largely replaced by sheets of blasts. Chromosomal analysis performed on the bone marrow aspirate showed an abnormal karyotype with the t(15;17) which was confirmed by FISH, monosomy 6 and a marker chromosome observed in 95% of the metaphase cells analyzed (46,XX,-6,t(15;17)(q24;q21),+mar[19]/46,XX[1]). A diagnosis of APLwith t(15;17)(q22;q21) PML/RARα was made.

Induction chemotherapy with ATRA, Cytarabine, Daunorubicin and etoposide was initiated. The patient developed skin flaking of her distal arms during the course of the induction therapy. Later, she received three cycles of consolidation therapy per COG protocol AAML06313 including arsenic trioxide. During the earlier consolidation period, she experienced rigors, chills, dizziness, nausea, vomiting, abdominal pain, and diarrhea concerning for sepsis. Antibiotics were promptly started which provided relief. During the late consolidation period, she developed severe neutropenia, thrombocytopenia, paronychia, felon, and cold sores requiring hospitalization and antibiotics. At the end of consolidation, bone marrow biopsy confirmed her remission status. She is now nearly one year from initial diagnosis and quantitative PCR for PML/RARα remains negative on maintenance therapy.

### 3.2. Case B

A 62-year-old Hispanic female was admitted due to complaints of petechiae and easy bruising. The laboratory studies on admission included a white blood cell count of 1.6 K/mm$^3$ (10% segmented neutrophils, 2% bands, 86% lymphocytes, and 2% basophils), a hemoglobin concentration of 11.6 g/dL, a hematocrit of 32.9%, a platelet count of 17 K/mm$^3$, a fibrinogen of 156 mg/dL, a D-dimer of 7430 ng/mL, an FDP of >80 μg/mL (reference range < 5 μg/mL), and normal blood chemistry tests and liver function tests. Additional laboratory studies included mildly elevated serum iron (153 μg/dL, reference range 35–140 μg/dL) and ferritin (468.7 μg/mL, reference range 11.0–306.8 μg/dL), and an elevated serum B12 level (2455 pg/ml, reference range 180–914 pg/mL), as well as normal PT, PTT, and urinalysis. Her bone marrow aspirate and biopsy showed markedly hypercellular (>90%) bone marrow composed predominantly of abnormal promyelocytes; Auer rods were easily found; faggot cells were noted. The morphologic features were typical for APL. Flow cytometric immunophenotyping of the blast population showed the blasts expressed CD13, CD33, CD117, and HLA-DR, without co-expression of T- and B-cell markers, CD11b, CD14, CD56, CD61, or TdT. Chromosomal analysis performed on the bone marrow aspirate showed an abnormal female chromosome complement in which an abnormal clone of cells (93%) contained a reciprocal translocation between chromosomes 15 and 17. A diagnosis of APL was confirmed.

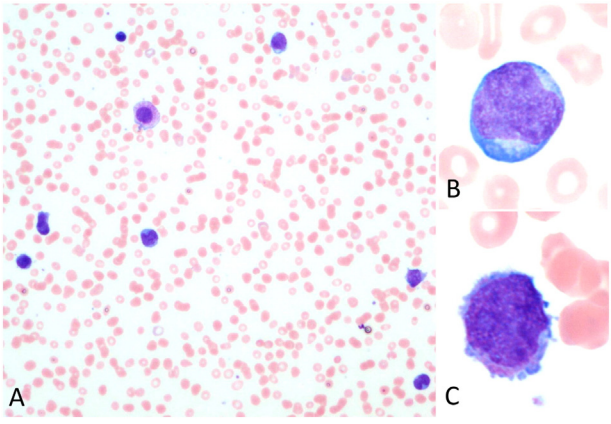


**Fig. 1.** Peripheral blood smear of case A reveals many blasts and occasional abnormal promyelocytes (A). The blasts contain small amounts of basophilic cytoplasm (B) sometimes with azurophilic granules (C). (Wright-Giemsa stain, original magnification, × 200 [A] and × 1000 [B, C]).