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CASE REPORT

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The curious case of HLA-DR-positive APL

Kanta Devi[1] | **Natasha Ali**[2]

[1]Department of Oncology, Aga Khan University, Karachi, Pakistan

[2]Department of Pathology and Laboratory Medicine/Oncology, Aga Khan University, Karachi, Pakistan

Correspondence
Natasha Ali, Department of Pathology & Laboratory Medicine/Oncology, Aga Khan University Karachi, Pakistan.
Email: natasha.ali@aku.edu

Abstract

The triad of weak/absent CD34, negative HLA-DR expression, and positivity to CD117 is pathognomonic for the diagnosis of acute promyelocytic leukemia. However, in rare cases, strong positivity to HLD-DR and CD34 may be noted.

KEYWORDS

APL, CD34 positivity, HLA-DR positivity, PML-RARα

1 | INTRODUCTION

To aid in prompt diagnosis of acute promyelocytic leukemia, flow cytometry is routinely performed to demonstrate the triad of weak/absent CD34, negative HLA-DR expression, and positivity to CD117. We report a case of 34-year-old female whose immunophenotyping results showed positivity to HLA-DR, CD34 and CD 117.

Acute promyelocytic leukemia (APL) with t(15;17)(q22;q21)/PML-RARα is a subtype of acute myeloid leukemia (AML) with distinct morphologic characteristics.[1] It can become aggressive and life threatening if there is a delay in recognition of the clinical presentation and diagnosis. Patients can develop coagulopathy leading to bleeding diathesis and death.[2] However, due to improvement in diagnostic modalities and early initiation of ALL-trans-retinoic acid (ATRA) and arsenic trioxide, the outcomes of dramatically improved. The definition of disease is through the detection of t(15;17)(q22;q21)/PML-RARα mutation, and this serves as the molecular basis of treatment with ATRA.[3]

The diagnosis of hematological malignancy especially in leukemia, after clinical history and physical examination, begins with performing complete blood count and review of peripheral smear. The classical morphology on peripheral smear of the abnormal promyelocytes reveals bilobed nucleus, abundant granules in the cytoplasm, presence of Auer rods, and faggot cells which is pathognomonic for APL.[4] Although confirmation is through molecular studies, to aid in rapid diagnosis, 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 (which belongs to human leukocyte antigen class II), and positive CD117.[5] Other features in flow cytometry 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.[6,7] HLA-DR-positive APL is a rare entity and has been scarcely reported. Mendoza et al[8] has described 45 cases of APL of which only two were HLA-DR-positive in which the clinical, morphological, and molecular characteristics were similar to HLA-DR negative APL.

Herein, we describe the case of a 34-year-old female who presented with clinical signs and symptoms of APL and immunophenotyping by flow cytometry analysis showed HLA-DR to be positive while PML-RARα mutation was also positive.

2 | CASE REPORT

A 34-year-old female presented to the emergency department of Aga Khan University Karachi, Pakistan, with complaints

of gingival bleeding, menorrhagia, and easy bruisability for one week. On examination, she had active oozing from gums and multiple, large bruises all over the body. There was no organomegaly. Baseline laboratory investigations showed Hb: 9.5 gm/dL, WBC: 21 × 10^9/L, platelets: 13 × 10^9/L. Peripheral blood film showed 75% abnormal promyelocytes with cytoplasm containing granules, Auer rods and faggot cells (Figure 1). Prothrombin time (PT) was > 170 seconds, INR > 17, activated partial thromboplastin time (APTT) was 43 seconds, fibrinogen was 35 mg/dL, and D-Dimer was > 30 mg/L FEU. Liver and renal function tests were within normal limits. Based on the findings of peripheral smear, immunophenotyping by flow cytometry (performed on BD FACSCanto™ analyzer, 8 color and 3 lasers) and molecular analysis of PML-RARα mutation was sent on peripheral blood. Bone marrow aspirate and trephine could not be performed at that time due to deranged coagulation parameters. Immunophenotype of the abnormal promyelocytes revealed positivity to CD4 (33%), CD13 (68%), CD33 (70%), cMPO (66%), HLA-DR (30%), CD117 (57%), CD34 (50%), CD36 (41%), and CD64 (66%) (Figure 2).

Due to the classical clinical and morphological findings, the patient was started on ATRA (45mg/m^2/day in 2 divided doses) and prophylactic dexamethasone 10mg once a day while we awaited molecular results. In 48 hours, the molecular analysis confirmed the presence of PML-RARα mutation. Her INR at that time became <1.5 and samples for bone marrow aspirate and cytogenetic analysis were drawn. Bone marrow morphology showed diffuse infiltration with abnormal promyelocytes. These cells were large with convoluted cytoplasm containing reddish pink granules and Auer rods (Figure 3). Since she was in the high risk category (WBC > 10 × 10^9/L), induction with daunorubicin and cytarabine (3 + 7 regimen) was started concomitantly while she received supportive care with 3 units of fresh frozen plasma (FFP) twice a day to keep INR less than 1.5 and D-Dimer less than 5 mg/L FEU. To maintain fibrinogen level of ≥200 mg/dL, 10 units of cryoprecipitate were transfused routinely. She also received platelet transfusion to sustain platelet count of ≥30 × 10^9/L. The WBC count after starting ATRA was gradually increasing from 21 to 35 to 45 × 10^9/L at which point capsule Hydroxyurea 1gm once a day was added.

Four days after starting ATRA she developed hemoptysis, tachypnea (respiratory rate 35/min), tachycardia (heart rate 120/min) and required noninvasive ventilation to maintain oxygen saturation of ≥95%. A differential diagnosis of ATRA syndrome was made and the drug was stopped. Chest X-ray revealed airspace shadowing (Figure 4) bilaterally with pulmonary edema. After stopping ATRA and adequate diuresis, her condition improved in 12 hours though chest X-ray findings improved over 24 to 48 hours. ATRA has been restarted at 50% dose while blood count recovery was awaited. Subsequently she was discharged after 28 days of induction chemotherapy. Her day-28 bone marrow revealed trilineage hematopoiesis with less than 5% blast cells while PML-RARα mutation was not detected. At present she has completed two cycles consolidation chemotherapy and is receiving maintenance treatment. Her PML-RARα mutation at the end of consolidation chemotherapy was not detected as well.

3 | DISCUSSION

Acute promyelocytic leukemia is characterized by clonal proliferation of abnormal promyelocytes. The World Health Organization's (WHO) classification recognizes the importance of genetic aberrations in the diagnosis and prognostication of AML and categorizes four unique groups of AML with recurrent chromosomal translocations out of which AML with t(15;17) is specific to APL. The others include AML with t(8;21) (q22;q22), AML with inv(16)(p13q22)/t(16;16)(p13;q22) and AML with 11q23 abnormalities. These four entities currently constitute about 25%-30% of all cases of adult AML.[9] Immunophenotyping by flow cytometry has become an essential tool for the lineage determination of leukemic blast cells. Various myeloid markers such as CD33, CD13, MPO, CD117, CD64, CD133, etc, are well recognized and useful for the confirmation of AML.[10]

The antigen HLA-DR is normally expressed on myeloblasts and loses expression at the promyelocyte stage of the maturation process. The absence of HLA-DR positivity is considered to be highly suggestive of APL and is used to distinguish AML from APL. In various studies published

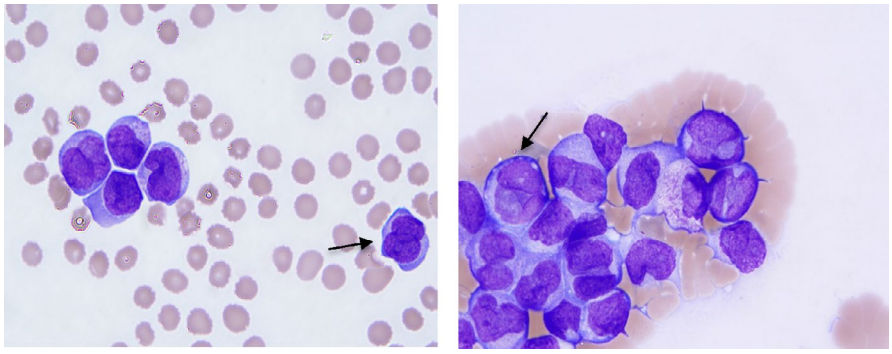

FIGURE 1 Peripheral blood film at (100×) showing abnormal promyelocytes and faggot cell

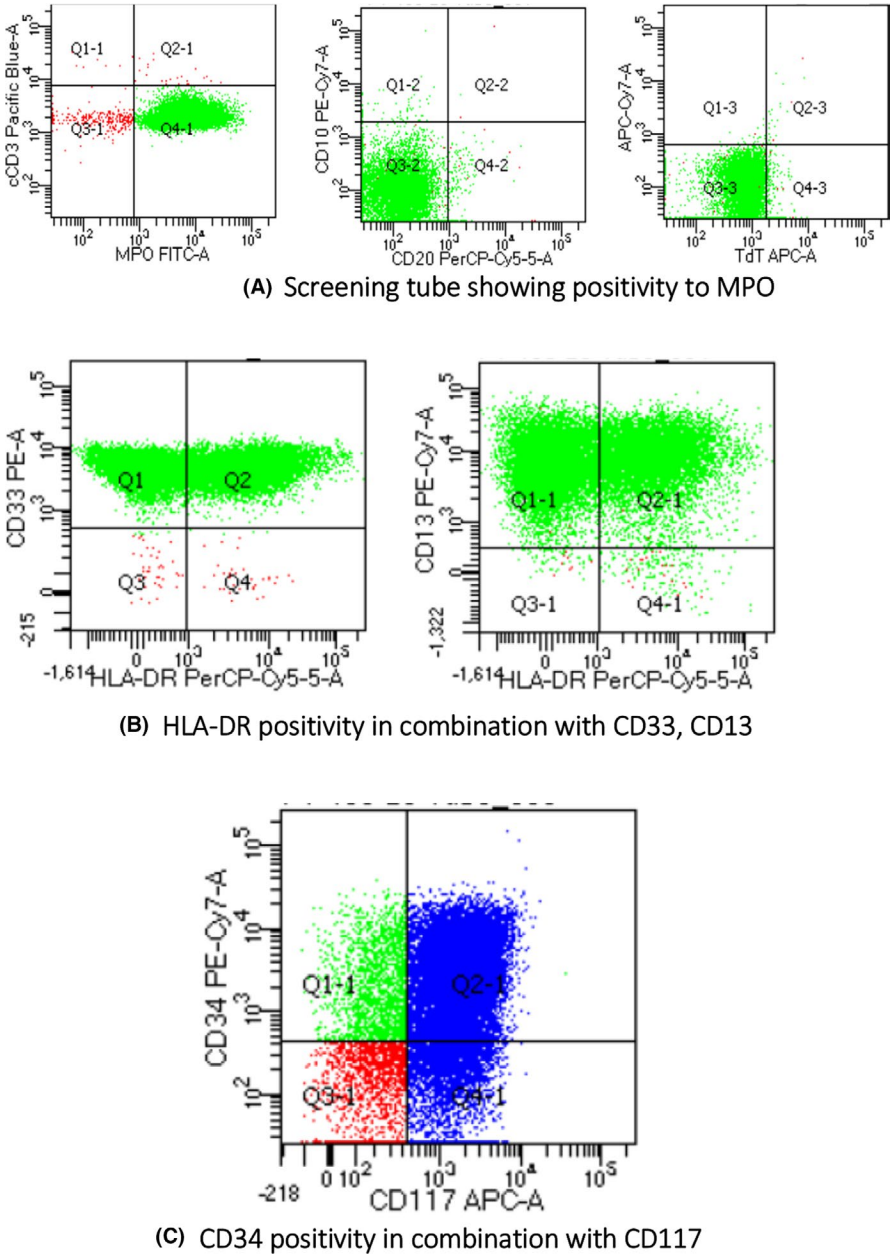

FIGURE 2 Immunophenotyping by flow cytometry showing positivity to HLA-DR and CD34. A, Screening tube showing positivity to MPO. B, HLA-DR positivity in combination with CD33, CD13. C, CD34 positivity in combination with CD117

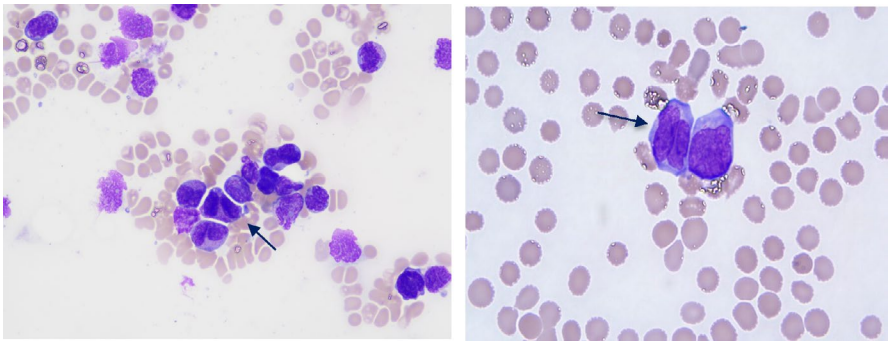

FIGURE 3 Bone marrow aspirate (100×) showing abnormal promyelocytes with bilobed nuclei

before, HLA-DR expression has been reported with a range of 0%-9%[11,12] of cases. The percentage of expression has also been variable in the studies reported, for example, Dong et al[13] reported only one case of APL with strong HLA-DR expression (20% or more) while four cases had a weak HLA-DR expression (staining 5%-20% of cells). In our case,

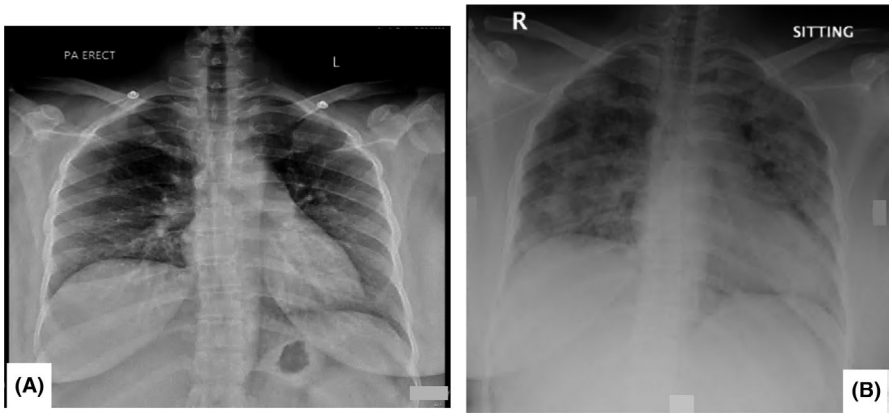

FIGURE 4 Chest X-ray findings – A, Normal chest X-ray on admission. B, bilateral airspace shadowing with pulmonary edema, with peripheral part of the lung being spared

the HLA-DR expression was very strong (30%) which rarely has been reported in literature. Along with HLA-DR expression, she also had positivity for CD34 (50%), which follows the same pattern of expression as HLA-DR, that is, negative expression on abnormal promyelocytes. CD34 positivity has been sparsely reported previously. Foley et al[14] has reported a cohort of 38 patients with APL, of which 32% of cases were CD34-positive and correlated with less differentiated APL blasts. In these patients, the incidence of early mortality is 50%. There is significant correlation between CD34 positivity and raised WBC count at presentation. Our patient also had similar parameters of HLA-DR and CD34 expression along with WBC count of 21 x 10^9/L at presentation.

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.[15] Moreover, while these investigations are pending, morphology supplemented by immunophenotyping helps in rapid diagnosis. In our case, although morphology was connotative of APL, flow cytometry indicated otherwise. Based on the symptoms, clinical presentation and deranged coagulation profile we still started ATRA and received conformation 48 hours later of APL though genetic analysis. This case consolidates the fact that with the advent of sophisticated automated diagnostic analyzers, morphological examination that is human eye dependent remains to be the backbone in leukemia diagnosis.

4 | CONCLUSION

In rare cases, APL can present with HLD-DR and CD34-positive immunophenotype. With a strong index of suspicion along with classical clinical and morphological findings, ATRA should be started in such patients while molecular analysis results are awaited. Although rarely reported, HLA-DR and CD34-positive cases present with high white blood cell count making them susceptible to increased induction mortality.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

KD – drafted manuscript, collection of data. NA – drafted manuscript, collection of data.

DATA AVAILABILITY STATEMENT

Not applicable.

ORCID

Natasha Ali https://orcid.org/0000-0003-4990-330X

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