Acute promyelocytic leukemia, hypogranular variant: a rare presentation

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Abstract

Early diagnosis of acute promyelocytic leukemia (APL) is essential because of its associated life threatening coagulopathy and unique response to all trans-retinoic acid (ATRA) therapy. The characteristic cell morphology supplemented by cytochemistry offers the most rapid means for diagnosis. Here we describe a rare case of acute promyelocytic leukemia-hypogranular variant that poses particular diagnostic challenge.

Introduction

Acute promyelocytic leukemia (APL), M3 subtype of acute myeloid leukemia (AML) is characterized in the majority of cases by proliferation of neoplastic hypergranlar promyelocytes and blast.[1] The biological and clinical heterogenicity of APL is based on the clinical presentation of the disease and various characteristics of leukemic cells at diagnosis. Patients with APL typically present with low white blood counts, peripheral blood cytopenias and coagulopathy.[2] A morphologic hypogranular variant is encountered with less frequent.[3] Here we report a case of APL- hypogranular variant that poses particular diagnostic challenge because of its atypical morphology.

Case Report

A 30-year-old male presented with severe anemia, bilateral subconjunctival haemorrhage and petechial skin rashes. Clinical examination revealed multiple ecchymosis, right cervical lymphadenopathy but no hepatosplenomegaly. Hematological examination showed a low hemoglobin count (9.0 gm%), total leucocyte count was markedly raised (80,000 cells/cu) with predominance of promyelocytes and blasts on differential count and platelet count of 34,000 cells/cu. Coagulation studies showed prothrombin time (PT) to be 15.2 s, activated partial thromboplastin time (APTT) -27.5 s and fibrinogen - 1.05 g/L. Chest X-rays and an echocardiogram were normal.

Peripheral blood cytomorphology showed promyelocytes with a characteristic bilobed or reniform nucleus; with majority of the cells either devoid of granules or contained only a few fine azurophil granules (Figure 1). The bone marrow aspirate was markedly hypercellular and frankly leukemic, 95% cells were blasts with bilobulated nucleus and fine dust like cytoplasmic granules. The leukemic cells showed a strong myeloperoxidase reaction (Figure 2). Molecular cytogenetic analysis by fluorescent in situ hybridization (FISH) was used to investigate chromosomal abnormalities associated with the leukemic process and found out to be translocation of chromosome 15 and 17, i.e., t(15;17) (Figure 3).

In view of the atypical blasts morphology, a provisional diagnosis of hypogranular variant of AML-M3v was suggested. The patient was immediately started on all trans-retinoic acid (ATRA) and cytarabine and is progressing well after 12 months of follow up period.

Discussion

This case report emphasizes the importance of a high index of suspicion for the diagnosis of acute promyelocytic leukemia, the hypogranular variant in particular. Overall, classical hypergranular and hypogranular variant constitute 5-8% of cases of AML in different Western Series,[4] and hypogranular variant comprises 1/3 of all cases of acute promyelocytic leukemia.[5] Both APL subtypes share a common pathogenic pathway, namely presence of t(15;17)(q21;q22) translocation and a similar clinical picture, namely consumptive coagulopathy at presentation (Table 1). They are responsive to differentiation therapy with all trans-retinoic acid (ATRA) and compete remission in seen in >80% cases.[6,7] Quite similarly

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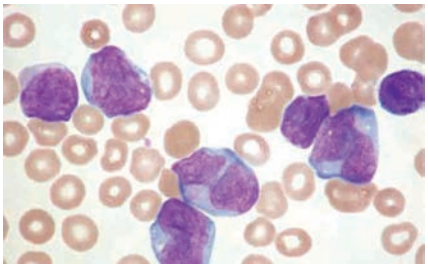

Figure 1. Peripheral blood film showing circulating promyelocytes with characteristically bilobed nucleus and hypogranular cytoplasm. Leishman stain x 1000.

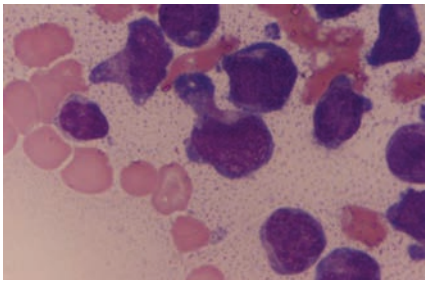

Figure 2. Cytochemistry result showing strong myeloperoxidase posi.

Table 1. A comparison of classical hypergranular and hypogranular variant.

	Hypergranular	Hypogranular
Definition	AML subtype in which maturation arrests in promyelocytic stage.	
Clinical	Disseminated intravascular coagulation/consumption coagulopathy	
WBC	Low	High
Nucleus	Round to oval	Bilobed
Cytoplasm	Densely packed large azurophilic granules, multiple auer rods, aggot cells.	Granules apparently absent, typical hypergranular promyelocytes exists in small number
Cytochemistry	Myeloperoxidase and Sudan Black-B strongly positive	
Immunophenotype	CD 33+, CD 34-/+, CD15-/+; CD 56-/+; HLA DR positive	CD 13+, CD 34+, HLA DR negative
Cytogenetics	t(15;17) (q22;q12)	

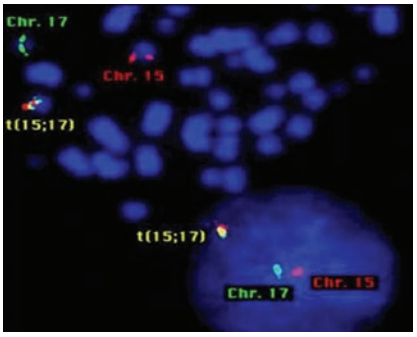

Figure 3. Acute promyelocytic leukemia: FISH technique shows chromosomal translocation, t(15;17).

our case is progressing well after 6 months of follow of period. Grignani *et al.*[8] have asserted that FISH is rapid and cost-effective when compared to classical cytogenetics, to establish diagnoses for the specific translocation t(15;17) in APL patients. Proper diagnosis of APL is critical for two reasons: i) anticipating complications due to disseminated intra-vascular coagulation (DIC) and ii) treatment with Tretinoin (all-trans-retinoic-acid) for complete remission in about 80% of patients.[7]

To conclude, the therapeutic option and prognostic implication in APL-variant has made early diagnosis of paramount clinical significance. Although, the cytogenetic and immunophenotypic signature should be referred to in diagnosing APL, from the practical point of view, other parameters, such as cytomorphology and cytochemistry are still important tools for rapid recognition of APL.

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