ZBTB16-RARα variant of acute promyelocytic leukemia with tuberculosis: a case report and review of literature

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INTRODUCTION

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML) with a defined clinical course and a biology that are distinct from other forms of AML [1]. Several key clinical features set APL apart, underlining the need for accurate diagnosis. These include a potentially devastating coagulopathy that carries a high risk of mortality, unless specifically addressed, and a sensitivity to retinoid-differentiating agents, including all-trans retinoic acid (ATRA), and to novel agents such as arsenic trioxide (As2O3) [2].

APL is typified by the t(15;17) translocation that leads to the formation of the PML/RARA fusion gene and predicts a beneficial response to retinoids. However, approximately 10% of APL cases lack the classic t(15;17). This group includes cases with cryptic PML/RARA gene rearrangements and a t(5;17) translocation that lead to the NPM/RARA fusion gene, which are retinoid-responsive, and cases with t(11;17)(q23;q21) that are associated with the ZBTB16/RARA (PLZF/RARA) fusion gene, which are retinoid-resistant. The ZBTB16/RARA cases are characterized by a predominance of blasts with regular nuclei, an increased number of Pelger-Huet-like cells, and CD56 expression [3].

Several hematological alterations ranging from various cytopenias to leukemoid reaction and even frank leukemia in association with tuberculosis have been reported [4]. To the best of our knowledge, this variant of APL with this clinical presentation and associated tuberculosis has not been reported so far. Here, we present a case of APL with morphological and cytogenetic studies compatible with the ZBTB16/RARA variant and tuberculosis.

CASE REPORT

A 23-year-old male presented with pulmonary tuberculosis and swelling of both lower limbs. He was put on antitubercular treatment. Hemogram showed mild anemia and Pseudo Pelger-huet cells. The bone marrow (BM) examination showed 52% promyelocytes with regular round to oval nuclei, few granules and were positive for CD13 and CD33, and negative for HLA-DR. Cytogenetic analysis of the BM aspirate revealed an apparently balanced t(11;17)(q23;q21). Final diagnosis rendered was acute promyelocytic leukemia (APL) with t(11;17)(q23;q21); ZBTB16/RARA. APL is a distinct subtype of acute myeloid leukemia. The variant APL with t(11;17)(q23;q21) cases that are associated with the ZBTB16/RARA fusion gene have been reported as being resistant to all-trans-retinoic acid (ATRA). Therefore, differential diagnosis of variant APL with t(11;17)(q23;q21); ZBTB16/RARA is very important. Here we have discussed the importance of distinct morphology of variant APL and also significance of rare presentation with tuberculosis.

Key Words ZBTB16-RARα variant, Tuberculosis, Promyelocytes
Fig. 1. Peripheral blood smear showing occasional promyelocyte (Leishman’s stain; magnification, ×1,000).

Fig. 2. Bone marrow aspirate showing promyelocytes having round to oval nuclei (May-Grunwald-Giemsa; magnification, ×1,000).

Fig. 3. Bone marrow aspirate showing promyelocytes having myeloperoxidase (MPO) positivity (MPO stain; magnification, ×1,000).

Fig. 4. Cytogenetic profile showing t(11;17)(q23;q21).

along with the occasional promyelocyte (Fig. 1). The coagulation profile was deranged with a positive D-dimer test. Doppler ultrasonography of the lower limbs was performed to rule out thrombosis and was non-contributory.

A bone marrow (BM) examination was conducted based on the presence of anemia and immature cells in the peripheral blood. BM aspirate and biopsy revealed hypercellular marrow spaces. The myeloid to erythroid ratio was 20:1 with 52% cells being promyelocytes. These promyelocytes had regular round to oval nuclei, a moderate amount of cytoplasm with few granules, and occasional Auer rods (Fig. 2) and were smaller than usual promyelocytes. However, cytochemical stains performed on the BM aspirate smear showed intense staining of most of these cells with myeloperoxidase stain (MPO, Fig. 3) and Sudan black B (SBB), confirming the promyelocyte morphology. Due to the massive maturation arrest, other causes related to infections and drug intakes were ruled out. This was important since drug-induced or Pseudomonas aeruginosa-induced agranulocytosis is characterized by a striking cohort of promyelocytes in the BM, which mimics promyelocytic leukemia [5].

Immunophenotyping revealed that the abnormal promyelocytes were positive for CD13 and CD33 and negative for HLA DR. Moreover, cytogenetics analysis of the BM aspirate showed an apparently balanced t(11;17)(q23;q21) in all 20 of the examined G-banded cells (Fig. 4). The final diagnosis rendered was APL with t(11;17)(q23;q21);ZBTB16/RARA.

The patient was lost to follow-up for 3 months after diagnosis and returned after taking ayurvedic medicines. The follow-up hemogram showed similar findings while he was receiving antitubercular therapy. His platelet count was still within normal limits, and D-dimer was still strongly positive. The patient refused chemotherapy and expired after 1 month.

**DISCUSSION**

The initial presentation of this case was active pulmonary tuberculosis with a high total leukocyte count and immature cells in peripheral blood. A leukemoid blood picture simulating acute myeloblastic leukemia has been previously described in association with disseminated tuberculosis [6], and in this case, BM and cytogenetic study confirmed the diagnosis of APL with t(11;17)(q23;q21). Retrospectively, the patient probably had an impaired immune response that caused reactivation of a latent focus of tuberculosis. Possible relationships between tuberculosis and blood dyscrasias can
include: (i) Activation and dissemination of latent tuberculosis focus due to loss of immune mechanism, particularly, cell-mediated immunity in BM failure and leukemia; (ii) Blood dyscrasias might be an unusual immunological response to tubercle bacilli [7].

APL is a distinct subtype of AML. Morphologically, it is identified as AML-M3 by the French-American-British classification. Cytogenetically, APL is characterized by a balanced reciprocal translocation between chromosomes 15 and 17, which results in the fusion of the promyelocytic leukemia (PML) gene and the retinoic acid receptor α (RARα). Variant chromosomal translocations (e.g., t(11;17), t(5;17)) can be detected in less than 2% of APL patients [8]. The present case exhibited morphological features similar to AML, which was confirmed to be an APL variant t(11;17) ZBTB16/RARA by cytochemical stains and cytogenetics. Of interest, APL cases with the variant t(11;17) ZBTB16/RARA show some morphological differences compared to APL with t(15;17) (q22;q12) (PML/RARα). This variant subgroup of APL has a predominance of cells that lack the characteristic bi-lobed or folded nuclei with many granules, the occasional Auer rods, and strong MPO reactivity. These cases have also demonstrated an increased number of pseudo-Pelger-Huet cells with strong MPO reactivity. Several cases of APL have been described in detail in the literature and are discussed below.

Kang et al. [9] reported 2 cases of acute myeloid leukemia with t(11;17) associated with varying morphology and immunophenotype. Their first case had a prominent monocytic component based on flow cytometric analysis and non-specific esterase staining of BM core biopsy touch preparations. Cytogenetic analysis of BM aspirate revealed 2 normal cells and 18 cells with an apparently balanced t(11;17)(q23;q21). The second case was more consistent with APL morphologically and immunophenotypically. The leukemic cells had a moderate amount of eosinophilic cytoplasm with numerous granules and Auer rods, and irregular nuclear contours with morphology similar to promyelocytes. These leukemic cells displayed strong positivity with MPO, SBB, and chloroacetate esterase stains. α-Naphthyl acetate esterase and α-naphthyl butyrate esterase stains revealed positive staining in less than 20% of the total BM cells. These morphological findings were similar to our case.

In APL with the variant t(11;17), the RARα gene on chromosome 17 fuses with the promyelocytic leukemia zinc finger gene ZBTB16 (PLZF) on chromosome 11 [9]. In another study conducted by Grimwade et al., 60 cases of APL were reviewed along with FISH analysis, reverse transcription/polymerase chain reaction (RT-PCR), and immunofluorescence. In 11 patients, APL was associated with ZBTB16/RARA rearrangement as determined by RT-PCR. The epidemiological survey revealed that ZBTB16/RARA accounted for approximately 0.8% of cases. Identification of this group is extremely important because of their poor response to retinoids as single-agent therapy and possible resistance to As2O3. However, it is clear from this study that complete response (CR) is attainable in this group with combination chemotherapy, indicating that cases of ZBTB16/RARA-positive APL are not necessarily associated with an adverse prognosis, as previously suggested [2].

In addition, Sainty et al. reviewed 67 cases of APL. The majority of cases (49) were due to insertion events with documented formation of PML/RARA. Of the 18 cases lacking a PML/RARA gene rearrangement, 11 cases possessed ZBTB16/RARA rearrangements [t(11;17)(q23;q21)]. There were 2 cases with t(5;17): a new case with t(5;17)(q34;q21), expressing NPM/RARA, and a case with an unbalanced der(5)t(5;17). Morphological analysis of the ZBTB16/RARA group showed that the majority of blasts had a regular nucleus and abundant cytoplasm with either coarse granules, or less frequently, fine or no granules. Only 2 cases exhibited faggots, a rare finding [3]. Licht et al. reviewed the clinical and molecular features of 6 patients with t(11;17)-associated APL. The clinical course of 3 patients was characterized by early death, and 3 experienced disseminated intravascular coagulation. All 6 patients had ZBTB16/RARA gene fusion as detected by RT-PCR, Southern blotting, or pulsed-field gel electrophoresis [10]. After a thorough literature search, no case of ZBTB16/RARA APML along with tuberculosis was found.

In conclusion, this case illustrates a rare presentation of ZBTB16/RARA along with tuberculosis, and the importance of correlating unusual features of promyelocytes, i.e., round-ed eccentric nuclei, few granules, and occasional Auer rods with pseudo-Pelger-Huet cells, while evaluating a case of APL. These features may indicate an underlying ZBTB16/RARA rearrangement. Additionally, leukemoid reactions closely simulating blastic leukemia, and in some cases, impossible to differentiate from true leukemia, have been reported in patients suffering from disseminated tuberculosis. Such a mode of presentation, though distinctly rare, is important to recognize as the treatment of these 2 diseases is entirely different, since this variant of APL is resistant to As2O3 and ATRA as a single-agent therapy.

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