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CASE REPORT

Acute promyelocytic leukemia with increased bone marrow reticulin fibrosis: Description of three cases and review of the literature

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Abstract
Pathologic increase in bone marrow reticulin fibrosis can be present in many malignant hematopoietic diseases. In acute leukemia, one-third of patients have some degree of marrow reticulin fibrosis at presentation, which is thought to be related to cytokine release from blasts. Marrow fibrosis is particularly common in acute megakaryoblastic leukemia, while this change is rarely seen in acute promyelocytic leukemia. Six case reports of acute promyelocytic leukemia with marrow reticulin fibrosis have been described so far in the literature. Herein, we present three cases of classical acute promyelocytic leukemia with increased marrow reticulin fibrosis encountered in our institution, summarizing their clinicopathologic features, treatment, and outcome to date. Awareness of the features of acute promyelocytic leukemia with marrow reticulin fibrosis is important as it may guide treatment options.

Introduction

Pathologic increase in bone marrow reticulin fibrosis can be seen in numerous malignant conditions [1]. In acute leukemia, around one-third of patients have some degree of mar-

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row reticulin fibrosis (MRF) at presentation. The increase in reticulin fibers in the marrow has been attributed to cytokine overproduction by leukemic cells expressing CD34 and HLA-DR [2]. The degree and occurrence of MRF vary significantly depending on the subtype of leukemia, with acute megakaryoblastic leukemia commonly showing an increase in marrow reticulin fibers, while acute promyelocytic leukemia (APL) rarely presenting with increased MRF [3,4]. To date, six cases of APL with MRF (APL-MRF) have been described in the literature. We herein present three cases of APL-MRF encountered at our institution over the course of 2 years, and we summarize their clinicopathologic features, treatment, and outcome, with a review of relevant literature.

Case presentations

Patient 1

The patient was a 28-year-old female who initially presented to an outside medical center with palpitations, headache, and dizziness. Peripheral blood counts showed a hemoglobin level of 8.9 g/dL, a platelet count of 122×10^9/L, and a leukocyte count of 2.1×10^9/L. Physical examination was essentially unremarkable. Her diagnostic work-up included flow cytometry immunophenotyping performed on peripheral blood that showed no evidence of malignancy, and a bone marrow core biopsy that was remarkable for severe reticulin fibrosis with no increase in blasts. The patient received blood transfusions and granulocyte-colony stimulating factor injections for 3 months without improvement in peripheral blood indices. She was then referred to our institution for further management. The outside bone marrow core biopsy was reviewed in our pathology department and showed an increase in immature cells with eosinophilic cytoplasm and with increased reticulin fibrosis (Fig. 1A and B). The atypical cells were diffusely positive for myeloperoxidase by immunohistochemistry, but negative for CD34. A repeat bone marrow aspirate was hypocellular but showed 55% blasts having hypergranular cytoplasm and numerous Auer rods, with ''faggot cells" being identified. Real-time polymerase chain reaction (RT-PCR) analysis performed on the bone marrow aspirate for PML-RARA fusion transcript was positive with a normalized copy number of 3,063. Mutations in *Jak2* and *MPL* genes were not detected. The overall findings were consistent with APL-MRF. The patient was subsequently started on arsenic trioxide (ATO) 0.15 mg/kg daily and all-trans retinoic acid (ATRA) 45 mg/m^2 daily. Post induction, a repeat bone marrow aspirate still yielded a dry tap, but a repeat bone marrow core biopsy showed a hypercellular marrow with atypical megakaryocytic hyperplasia and increased reticulin fibrosis (Fig. 1C and D). A repeat RT-PCR for PML-RARA after induction therapy with ATO and ATRA was low positive with

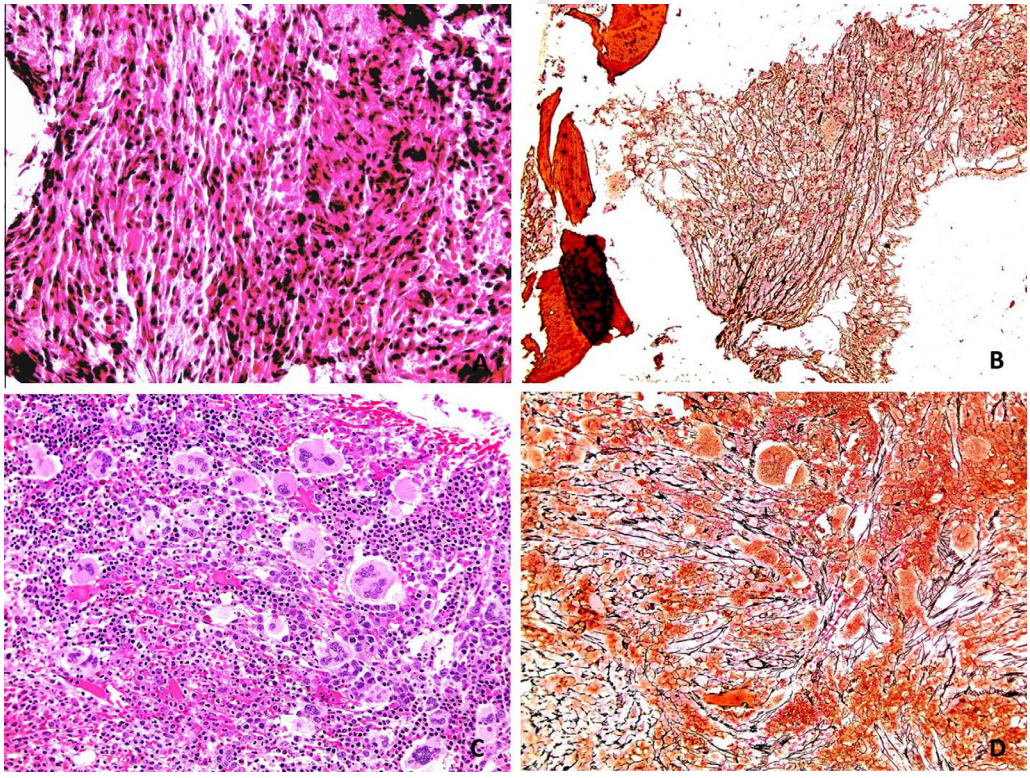

Fig. 1 Patient 1. Suboptimal bone marrow core biopsy at initial diagnosis (received for consultation), with marginal preservation of morphology, showing a diffuse population of atypical cells with (A) moderate eosinophilic cytoplasm (hematoxylin and eosin, 200×) and (B) increased reticulin fibrosis (reticulin special stain, 100×). Follow-up bone marrow core biopsy after treatment (1 month after diagnosis) with no evidence of acute leukemia, but with (C) increased cellularity and atypical megakaryocytic hyperplasia (hematoxylin and eosin, 200×) and (D) increased reticulin fibrosis (reticulin special stain, 200×).

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