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Unusual massive bone marrow fibrosis in acute promyelocytic leukemia following arsenic trioxide therapy

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ABSTRACT

Bone marrow fibrosis has been associated with different types of non-neoplastic conditions like granulomatous and autoimmune diseases and a variety of neoplastic disorders such as acute megakaryoblastic leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma and myeloproliferative neoplsms. Therapy induced fibrosis is a rare phenomenon. Here we report a case of an incidentally diagnosed acute promyelocytic leukemia (APL) with *t*(11;17) which was treated with arsenic trioxide (ATO) for 45 days. However, the patient did not go into remission and developed massive fibrosis of bone marrow. Literature search does not reveal such documented marrow fibrosis following therapy with ATO in a case of APL.

Introduction

Bone marrow fibrosis is known to occur in several neoplastic and non-neoplastic conditions. Among neoplastic conditions such as acute leukemia, it is most often seen with acute megakaryoblastic leukemia [1]. Acute promyelocytic leukemia (APL) presenting with marrow fibrosis is a rare entity, with few cases reported in the past [2–4]. In one case series a reversible bone marrow collagenous fibrosis has been reported in cases of APL treated with tretinoin [5]. However literature search did not reveal any such occurrence of bone marrow fibrosis following therapy with arsenic trioxide (ATO) in a case of APL. Here we report a case of 44 year old female who was diagnosed as APL with *t*(11;17), who subsequently developed bone marrow collagenous fibrosis following induction therapy with ATO.

Case history

A 44 year old female, known hypothyroid and hypertensive on regular medication, presented with spontaneous skin bleed for five months, generalized weakness, fatigability and menorrhagia for three months duration. She was diagnosed to have fibroid uterus and underwent diagnostic dilatation and curettage (D&C) for her complaints at an outside hospital. As her bleeding per vaginum did not stop after D&C, hysterectomy was performed. During the post operative period she was found to have high total leukocyte count (TLC). Subsequently the patient developed pain abdomen, found to have hemoperitoneum and exploratory laparotomy was carried out to achieve hemostasis. Since she had high TLC, bone marrow examination and cytogenetics were carried out which revealed abnormal promyelocytes and 45*X*, −*X*, *t*(11;17)(q23;q21) respectively (Fig. 1). Based on the morphological and cytogenetic abnormality, diagnosis of APL was made and the patient was transferred to our center for further management. On examination she had pallor, fever, multiple purpuric spots over upper and lower limbs, a midline abdominal suture wound with gaping and necrotic slough along with foul smelling discharge. Respiratory system examination revealed diminished breath sounds in left infrascapular region suggestive of pleural effusion. CT scan chest showed bilateral ground glass opacities suggestive of fungal pneumonia and left sided pleural effusion. There was no organomegaly or peripheral lymphadenopathy. Laboratory parameters revealed hemoglobin of 69 g/L, TLC of 35.39×10^9/L with a differential leukocyte count of 50% promyelocytes, 19% myelocytes, 01% metamyelocyte, 27% mature neutrophils, 03% lymphocytes and platelet count of 44×10^9/L. After admission to our center, her

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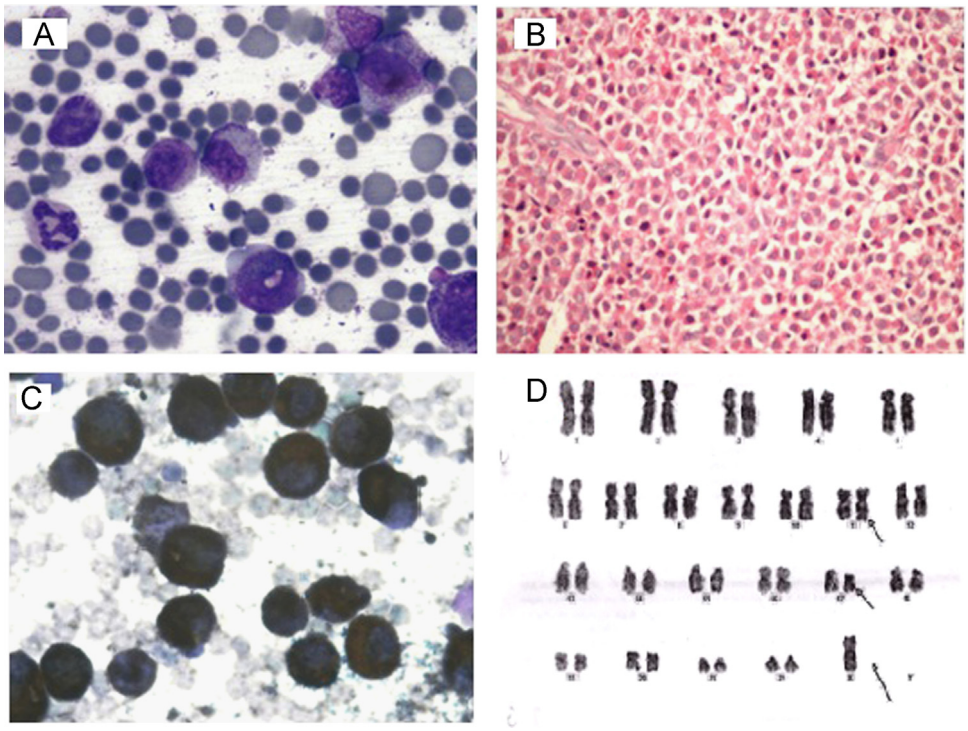

Fig. 1. Bone marrow aspirate – blast, promyelocyte along with mature myeloid cells (A, Jenner Giemsa stain, × 1000). Bone marrow biopsy showing diffuse replacement by immature myeloid cells with no fibrosis. (B, Hematoxylin & Eosin stain, × 400). Bone marrow aspirate – strong MPO positivity (C, myeloperoxidase stain, × 1000). Karyogram showing 45*X*, −*X*, *t*(11;17)(q23;q21) (D, karyotype).

coagulation parameters remained within normal limits and there was no laboratory evidence of disseminated intravascular coagulation. Bone marrow examination revealed 45% hypergranular promyelocytes with 03% blasts, 40% maturing myeloid forms and neutrophils, 06% erythroid cells and 06% lymphocytes. There were no Auer rods or fagot cells seen. Myeloperoxidase stain showed strong MPO positivity in these promyelocytes. The bone marrow biopsy showed near total replacement by immature myeloid forms without marrow fibrosis (Fig. 1). In view of foci of infections involving lung and gaping infected wound in anterior abdominal wall, patient was not offered Inj daunorubicin and all trans retinoic acid. Instead she was started on ATO at a dose of 0.15 mg/kg body weight along with supportive antibiotics and antifungals. During therapy she became afebrile, her abdominal wound healed and lung lesions resolved. The TLC reduced gradually along with signs of maturation in the peripheral smear. However by day+45, patient developed pancytopenia and hence bone marrow examination was performed to assess the disease status. Bone marrow aspiration yielded a dry tap and the bone marrow biopsy tissue obtained was pale and gray white on gross examination. The peripheral smear received along with the bone marrow revealed an occasional promyelocyte and the bone marrow aspirate smears were paucicellular which revealed 03% blasts, 08% promyelocytes, 11% myelocytes, 07% metamyelocytes, 10% neutrophils and 61% lymphocytes. The bone marrow biopsy tissue revealed dense diffuse marrow fibrosis with extensive collagen deposition suggestive of grade III marrow fibrosis [6] confirmed on Masson trichrome stain, with entrapped immature myeloid forms of similar morphology observed in the diagnostic marrow (Fig. 2). The therapy with ATO was discontinued in view of bone marrow fibrosis and patient was observed with supportive care. Subsequently, on follow up the TLC and promyelocyte count in peripheral smear increased in number. As the patient did not have any foci of infection, she is now started on induction chemotherapy with daunorubicin and all-trans retinoic acid.

Discussion

Bone marrow fibrosis is known to be associated with hematolymphoid malignancies such as acute leukemia, Hodgkin and non-Hodgkin lymphoma. Among the acute leukemias, marrow fibrosis is most often seen with acute megakaryoblastic leukemia. It is an uncommon finding in APL and till date only handful of case reports are seen in literature, however its presence does not seem to alter the prognosis of APL [4,7]. Hatake et al. demonstrated bone marrow fibrosis following therapy with tretinoin and also proved that the fibrosis is reversible after stopping tretinoin and chemotherapy [5]. However there is no reports so far mentioned in literature regarding marrow fibrosis post ATO therapy, hence our case would be the first of its kind with this unique finding. In APL ATO has dose dependant effect on promyelocytes inducing preferential apoptosis at high concentration (0.5–2 μmol/L), inducing partial differentiation at low concentration (0.1–0.5 μmol/L) and causing modulation and degradation of PML-RARα protein at a dose of 0.1–0.2 μmol/L [8]. Mori et al. suggested a possible role of transforming growth factor beta (1) (TGF-β1) in causing the fibrosis in APL as they have noticed the overexpression of TGF-β1 by RT-PCR [2]. A similar mechanism is possible with ATO in inducing bone marrow fibrosis as brought out by Chu et al. who had established the role of ATO-induced TGF-β1secretion from cardiac fibroblasts which resulted in myocardial fibrosis [9]. In the same line Szymańska-Chabowska et al. demonstrated the role of arsenic in liver fibrosis leading to chronic hepatic failure [10]. Hence it can be said with reasonable confidence that, as ATO is capable of inducing fibrosis in heart and liver, it is possible for ATO to induce bone marrow fibrosis as well even though it is not mentioned in literature so far. Whether this ATO induced fibrosis in unique to the

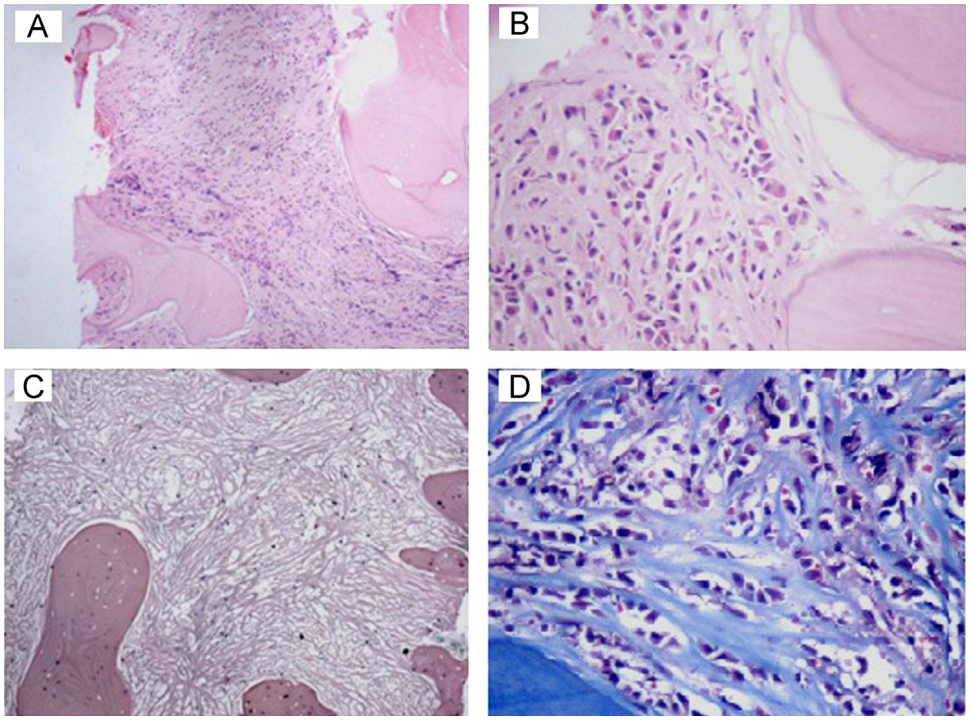

Fig. 2. Bone marrow biopsy showing diffuse fibrosis with collagenisation along with entrapped immature myeloid cells (A – Hematoxylin & Eosin stain, × 100, B – Hematoxylin & Eosin stain, × 400, C – reticulin stain, × 100, and D – Masson trichrome stain, × 400).

cytogenetic abnormality this patient has, needs to be explored. Also the outcome of this marrow fibrosis needs to be ascertained from further follow up of this patient. As RT-PCR for PML-RARα will not help in this case to assess the molecular remission, the patient needs to be followed up with conventional cytogenetics or FISH analysis for molecular remission status. This case had so many unusual features such as a long duration of illness, uncommon morphological findings, rare cytogenetic abnormality and ATO induced bone marrow fibrosis. Hence the case is reported for this constellation of unique features.

Source of support

None.

Conflict of interest

None.

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