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Case report

An unusual case report of myelofibrosis following treatment for acute promyelocytic leukemia with myeloid sarcoma as the initial manifestation

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ABSTRACT

Introduction: Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML), with myeloid sarcoma (MS) seldom occurring at onset. Myelofibrosis (MF) is a condition characterized by megakaryocytic proliferation and atypia with an array of clinical findings, but MF secondary to APL treatment is extremely rare. MF secondary occurring after treatment of APL with MS as the initial presentation has not been reported.

Case report: A 73-year-old male was admitted to our hospital in August 2016, presenting with a pain in his left shoulder, followed by right shoulder and bilateral hip pain. A progressive increase in a mass in the right sternoclavicular joint was also observed. After comprehensive examines, he was diagnosed as APL with MS as the initial manifestation in April 2017. The patient then underwent induction, consolidation, and maintenance therapies until August 2019 and achieved complete remission. However, twice examinations in December 2020 and September 2022 confirmed that MF was present.

Conclusion: This is the first case of MF secondary occurring after treatment of APL with MS. Early recognition of MS in APL patients is crucial for timely intervention and treatment initiation. Meticulous diagnostic work-up and careful monitoring during treatment are necessary to detect potential complications, which may significantly impact the patients' outcome. Also, a comprehensive management approach encompassing induction, consolidation, and maintenance therapies should be adopted to ensure optimal therapeutic responses and reduce the risk of recurrence or treatment-related complications.

1. Introduction

Acute promyelocytic leukemia (APL), accounts for only 5–10 % of all AML cases and its diagnosis poses a significant hematological challenge [1], typically presents with symptoms related to aggressive onset and disseminated intravascular coagulation (1). It is characterized by the proliferation of abnormal promyelocytes in the bone marrow and the presence of PML/RARα fusion gene caused by a specific chromosomal translocation t (15; 17) [2,3]. Myeloid sarcoma (MS), also known as granulocytic sarcoma or chloroma, is an

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extramedullary tumor consisting of immature myeloid cells [4]. Although MS has been reported in 2%–10.4 % of AML patients, it is predominantly associated with AML FAB M2, M4, and M5 subtypes and is seldom observed in patients with APL at onset [5]. Myelofibrosis (MF), a condition characterized by megakaryocytic proliferation and atypia, can present with an array of clinical findings such as anemia, constitutional symptoms, hepatosplenomegaly, or thrombosis [3,4], and is usually associated with mutations such as JAK2V617F, CALR, or MPL [6]. Although MF is known to transform into AML after treatment [7], the development of MF secondary to APL treatment is extremely rare, with only two cases reported in the literature to date [8,9]. MF secondary occurring after treatment of APL with MS as the initial presentation has not been reported, underscoring the uniqueness of the case represented in this report. Herein, we describe a 73-year-old male who presented with MS as the initial manifestation of APL and later developed MF following treatment. This unique case provides insights into the complexity and challenges in diagnosing and managing APL with MS at onset and raises awareness of the potential for secondary MF development following treatment.

2. Case report

A 73-year-old male was admitted to our hospital in August 2016, presenting with a pain in his left shoulder, followed by right shoulder and bilateral hip pain. There was no family history of cancer or exposure to harmful carcinogens. The patient did not accept any interventions before. A progressive increase in a mass in the right sternoclavicular joint was also observed by physical examination upon arrival. Routine blood examination showed a hemoglobin (Hb) level of 115g/L, a white blood cell (WBC) level of 6.6 $\times$ 10^9/L with a neutrophilic granulocyte percentage of 76.3 %, a platelets (PLT) count of 278 $\times$ 10^9/L. Magnetic resonance imaging (MRI) revealed multiple bone abnormalities, suggesting the possibility of malignant tumors. Immature cells were observed by H&E stain of the right iliac bone biopsy (Fig. 1A). Immunohistochemical (IHC) analysis of the right iliac bone showed positive staining for MPO (Fig. 1B), CD99, Fli 1, weak positive staining for CD117 (Fig. 1C), and partly positive staining for PGM1, but negative staining for CD34 (Fig. 1D), CD3, CD20, CD56, CD138, Syn, CgA, FFT1, CK, EMA, PSA, PsAP, CK5/6, and PAS; and proliferative activity index (Ki-67) was 15 %. The above results of right iliac bone biopsy hinted a suspicion on myeloid leukemia or MS. On April 7, 2017, positron emission tomography–computed tomography (PET/CT) analysis of the whole body disclosed high metabolic focus of soft tissue density in front of the right sternoclavicular joint, involving the adjacent manubrium sternum (SUVmax = 6.4); and multiple diffuse bone density increase in the shoulders, lumbar vertebrae, pelvis, and bilateral upper femurs (SUVmax = 3.5) (Fig. 2A and B).

Routine blood examination on April 17, 2017 showed a Hb level of 90 g/L, a WBC level of 3.8 $\times$ 10^9/L with a neutrophil percentage of 38.4 %, and a PLT count of 97 $\times$ 10^9/L. Bone marrow morphology showed: myeloblasts accounted for 21 %, with small cell bodies, regular nuclei, thin chromatin and visible nucleoli; and a small amount of cytoplasm presenting dusty blue fluorescence with granules in the cells was observed (Fig. 3A). Immunophenotyping showed 53.4 % immature cell population that were positive for CD33 and CD117. Fluorescence in situ hybridization (FISH) analysis demonstrated PML-RARα fusion (Fig. 3B). Chromosome karyotype analysis revealed 47, XY, t (15; 17)(q24; q21), +21 [4]/46, XY [3]. No abnormalities were found in AML mutation panel detected by next-generation sequencing. Of note, the sequencing results also showed no mutations in MF-related genes, including CALR, JAK2 and MPL.

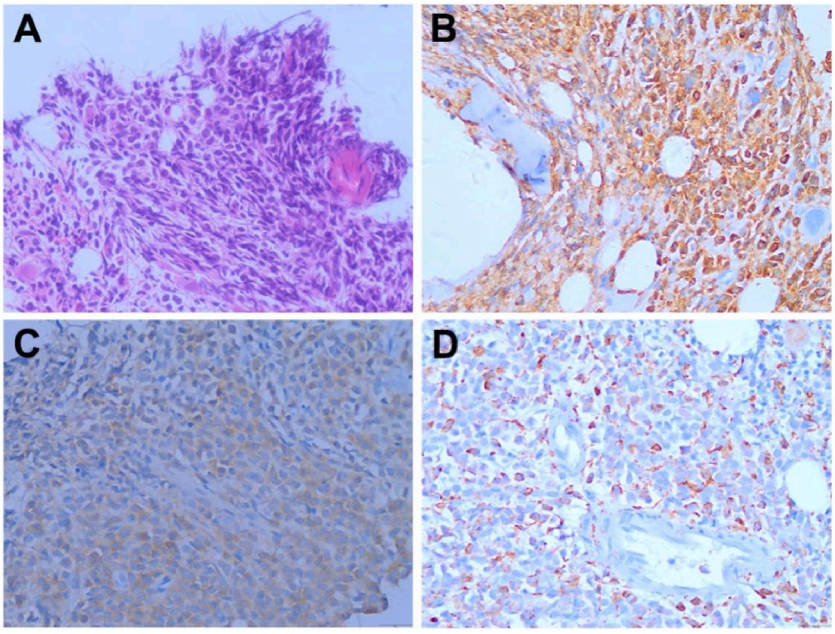

Fig. 1. (A) H&E stain of the right iliac bone biopsy ($\times$ 400). (B–D) Histological analysis of the right iliac bone ($\times$ 400) showing positive staining for MPO (B), weak positive staining for CD117 (C), but negative staining for CD34 (D).

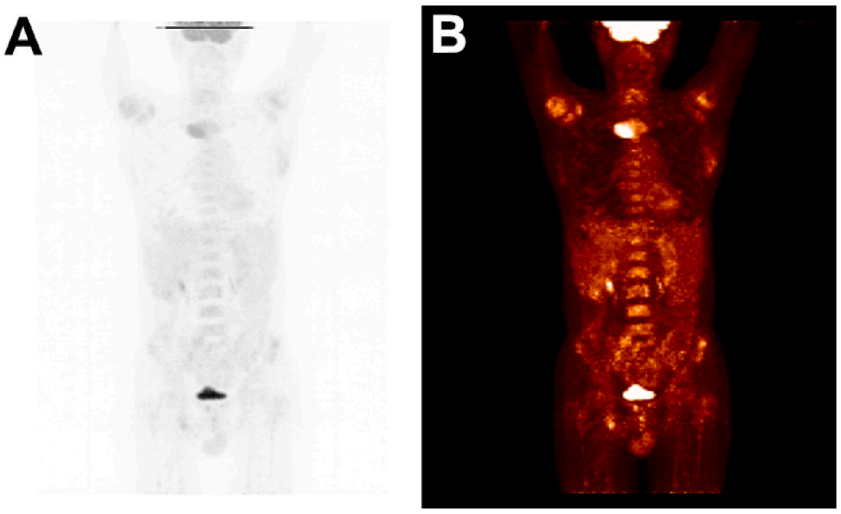

Fig. 2. (A and B) PET/CT analysis of the whole body disclosed high metabolic focus of soft tissue density in front of the right sternoclavicular joint, involving the adjacent manubrium sternum; and multiple diffuse bone density increase in the shoulders, lumbar vertebrae, pelvis, and bilateral upper femurs.

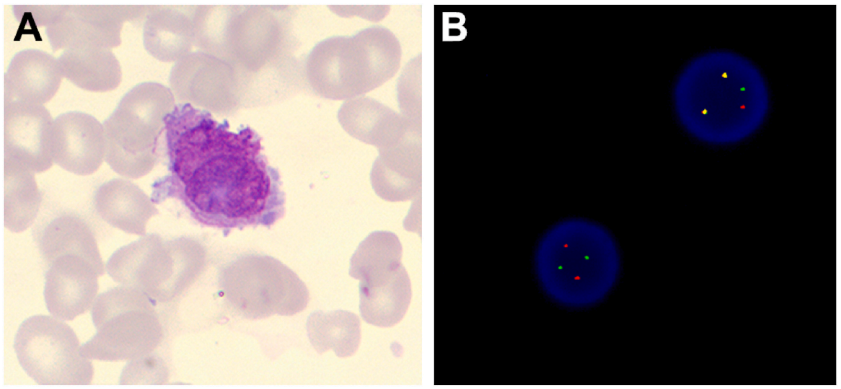

Fig. 3. (A) Bone marrow morphology analysis showing myeloblasts with small cell bodies, regular nuclei, thin chromatin and visible nucleoli. (B) FISH analysis in the bone marrow sample demonstrated PML-RARα fusion.

Considering the patient's clinical manifestations, bone marrow morphology, imageological, chromosomal, cytogenetic examination results, the diagnosis of APL with MS as the first presentation was made. The patient was started on pharmacological induction therapy with all-trans retinoic acid (ATRA, 10 mg, tid, d1-28), arsenic trioxide (ATO, 0.16 mg/kg, qd, d1-28) and idarubicin (5 mg, d1, 3, 5, 7) on April 25, 2017. During the treatment, the patient experienced acute left heart failure, differentiation syndrome, liver dysfunction, and pulmonary infection, but improved after treatment. Bone marrow morphology on June 21, 2017 showed complete remission (CR). Then, the patient received consolidation therapy with ATO (0.16 mg/kg, qd, d1-28) followed 1 month later by oral administration of ATRA (10 mg, tid, d1-14). Bone marrow examination on Oct 5, 2017 showed CR, with normal chromosomal karyotype, and negative minimal residual disease (MRD) and PML/RARα fusion. The patient then received consolidation chemotherapy of HAG regimen (homoharringtonine 1mg, qd, d1-14; cytarabine 10 mg/m^2, q12h, d1-14; granulocyte colony stimulating factor, 300 μg/d, from d0, adjusted according to WBC level) from October 12, 2017, followed by ATRA (10 mg, tid) for another 14 days from November 15, 2017. PET-CT examination showed diffuse uneven glucose metabolism in the bone marrow (SUVmax = 1.9). He was then given alternating maintenance therapy with ATRA and ATO, and underwent lumbar puncture and intrathecal chemotherapy several times to prevent central nervous system involvement. Cerebrospinal fluid examination showed no significant abnormalities. Several times of bone marrow examinations showed CR, with normal chromosomal karyotype, and negative MRD and PML-RARα fusion. The treatment was completed in August 2019, and the patient showed good intervention adherence and tolerability during the whole treatment duration.

In December 2020, routine blood examination showed that Hb: 131g/L, WBC count: 10.5×10^9/L (79.8 % neutrophils) and PLT count: 211×10^9/L. Bone marrow morphology showed CR with a negative MRD. Chromosomal analysis revealed 46, XY, t (12; 13) (q14; q12) [4]/46, XY [6]. PML/RARα fusion gene was not detected in the bone marrow sample by FISH, but positive mutations in

CALR, TET2, BRCA2, and KMT2D were detected by gene examination. And the levels of variant allele fraction of CALR, TET2, BRCA2 and KMT2D were 34.30 %, 47.90 %, 48.20 % and 4.00 %, respectively. Bone marrow biopsy revealed active bone marrow hyperplasia with fibrosis (MF Grade 2), and increased granulocyte-to-erythrocyte ratio (5:1) and megakaryocytes. The patient underwent a re-examination on September 26, 2022. Routine blood examination showed a Hb level of 105 g/L, a WBC level of 4.7 × 10^9/L with a neutrophil percentage of 82.9 %, and a PLT count of 134 × 10^9/L. Bone marrow morphology showed CR with a negative MRD. Chromosomal analysis revealed 46, XY, t (12; 13)(q14; q12) [6]/46, XY [4] (Fig. 4A). FISH analysis did not detected PML/RARα fusion gene, but molecular testing showed a CALR mutation. Bone marrow biopsy showed active bone marrow hyperplasia, with increased granulocyte-to-erythrocyte ratio (6:1) (Fig. 4B). The various stages of granulocytes and erythroid cells are visible. Additionally, increased megakaryocytes, scattered or clustered distribution, with "balloon" shape were observed. Besides, fibrous tissue hyperplasia was confirmed by reticular fiber staining (MF Grade 3) (Fig. 4C). IHC analysis showed CD34 (individual cells+), CD117 (individual cells+), CD15 (granulocyte cells+), CD68 (monocyte cells+), MPO (granulocyte cells+), CD99 (individual cells+), Lysozyme (granulocyte cells+), CD235a (erythroid cells+), Ki67 (+), and CD42b (megakaryocyte cells+). The above results suggests that the bone marrow hyperplasia was active, the megakaryocyte morphology was abnormal, and bone marrow fibrosis was present. The calculated risk scores for MF (IPSS, DIPSS and DIPSS plus) were all 1 point. The patient had moderate splenomegaly (spleen palpation was 4 cm subcostal at the left margin),but had no significant clinical symptoms, no severe anemia, and no significant increased WBC count and PLT count. After assessment by the clinician, the patient did not undergo further treatment,and is currently under follow-up.

3. Discussion

MS can develop in relapse cases, especially after APL treated with ATRA, but it rarely occurs in APL at onset [10]. AML transforming from MF after treatment is frequently reported, while MF secondary to APL treatment is extremely infrequent. The present case underscores an unusual clinical scenario, a manifestation of MF post-treatment for APL with MS as the initial presentation. The confluence of these three hematological disorders in a single patient has not been reported, highlighting the rare and complicated occurrence of MF following the treatment of APL with MS as the initial manifestation, and providing valuable insights regarding the diagnosis, management, and possible outcomes of such complex hematologic conditions. However, due to the unimplemented treatment for MF, we are not clear about the prognosis of such secondary MF.

MS is a rare extramedullary tumor constituted by immature myeloid cells. It can occur in a patient with AML [11] and chronic myeloid leukemia [12]. The patient's initial presentation with MS preceding the diagnosis of APL is atypical since MS rarely occurs in APL at onset. Two recent studies have summarized the literature of APL with MS as the initial presentation published so far; no more than 30 cases are included [5,13]. It was found that this type of leukemia affects patients at a wide age range (1–77 years old), and sex-bias phenomenon was difficult to explain due to the limited number of patients. The most common sites of APL with MS are spine, skin and tongue, followed by the testis, axilla, breast, cerebellum, colon, femur, tibia, mandible, oral cavity, ovary, pelvis, rectum, and thymus. Most APL with MS cases did not present with characteristic hemorrhage of APL. The diagnosis of APL with MS as the primary manifestation was a challenge. A small number of cases are first misdiagnosed as a lymphoma or Ewing sarcoma due to insufficient immunophenotyping of the tumor tissue [14,15]. Therefore, proper histological, flow cytometric, cytogenetic, chromosomal analyses and imageological examinations are essential for the correct diagnosis.

The patient's subsequent development of MF post-APL treatment is a noteworthy event. MF is more common in AML [16],chronic myeloid leukemia [17], and other diseases. However, only two cases of MF secondary to APL treatment have been reported [8,9]. In their cases, they did not report any initial presentation of MS. Therefore, the development of MF post-treatment for APL with MS as the initial presentation in this patient is another rare occurrence. The present case thus broadens the spectrum of potential intricacies in the clinical course of a patient diagnosed with APL. It also serves to elucidate the nuances of disease progression, the potential correlation among APL, MS and MF, and the probable effect of a prior hematological malignancy on the clinical outcome of a subsequent one.

It has been reported that both ATRA and ATO may cause MF during treatment. Venkatesan reported a patient with APL who was treated with ATO alone. On the 45th day after ATO treatment, bone marrow puncture showed obvious dry tap, and the biopsy results indicated severe MF (grade 3) [9]. Hatake observed 13 patients with APL, without MF at the initial diagnosis. After ATRA treatment, 11 of them had collagen fibers in their bone marrow, and MF was relieved to varying degrees after ATRA withdrawal or consolidation chemotherapy [8]. In primary MF models, oral active retinoic acid receptor antagonists may restore normal platelet production and bone integrity and significantly reduce fibrosis [18]. In the current case, no MF-related symptoms and gene mutations were found

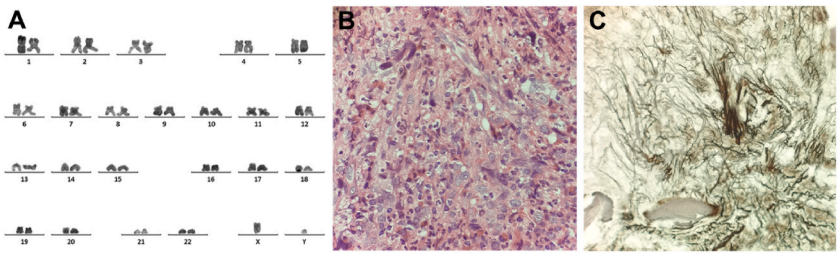

Fig. 4. (A) Chromosome karyotype: 46, XY, t (12; 13)(q14; q12) [6]/46, XY [4]. (B) H&E stain of the bone marrow biopsy (× 400). (C) Bone marrow biopsy showed extensive fibrous tissue hyperplasia (MF grade 3) (× 400).

before the treatment of APL, excluding the co-exist of MF and APL at the initial diagnosis. However, MF along with abnormal megakaryocytes was observed in bone marrow biopsy after the successful treatment and remission of APL with ATRA, ATO and idarubicin. Moreover, the appearance of t (12; 13) translocation and positive mutation in CALR confirmed the occurrence of MF after treatment of APL. It is essential to consider the possible mechanisms that could have led to the development of MF in this patient following APL treatment. One hypothesis is that APL therapy might have caused some genetic or epigenetic alterations, leading to clonal expansion of abnormal megakaryocytes, and subsequent MF. Another possibility is that MF may have evolved from a pre-existing undiagnosed myeloproliferative neoplasm, which could have been masked by APL or MS in the initial stages.

4. Conclusion

This case of MF following treatment for APL with MS as the initial manifestation showcases the complexity and challenges in diagnosing and managing such rare hematologic conditions, hinting that early recognition of MS in APL patients is crucial for timely intervention and treatment initiation. Additionally, eticulous diagnostic work-up and vigilant monitoring during APL therapy, since the development of secondary MF might lead to poorer outcomes and an adverse impact on the patients' quality of life. Moreover, in patients with APL and MS at onset, a comprehensive management approach encompassing induction therapy, consolidation, and maintenance should be adopted to ensure optimal therapeutic responses and reduce the risk of recurrence or treatment-related complications. This case highlights the necessity to remain vigilant to uncommon presentations of hematologic malignancies, as they may provide valuable insights into the disease pathogenesis, management, and clinical course.

CRediT authorship contribution statement

Qiaoyan Han: Writing – original draft, Investigation, Funding acquisition, Data curation, Conceptualization. **Sheng Wu:** Writing – original draft, Data curation. **Yefei Zhang:** Writing – original draft, Data curation. **Jiao Lu:** Data curation. **Xin Jiang:** Data curation. **Miao Sun:** Writing – review & editing, Project administration.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author. Data will be made available on request.

Ethics statement

This study was approved by the Medical Ethics Committee of Jingjiang People's Hospital. Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e39144.

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