Thrombocytosis in a patient with acute promyelocytic leukemia during treatment with all-trans retinoic acid and arsenic trioxide

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Abstract

Thrombocytosis, an uncommon side effect of all-trans retinoic acid (ATRA) treatment, occurs in some patients with acute promyelocytic leukemia. Our case showed thrombocytosis on day 26 to day 32 of ATRA and arsenic trioxide therapies and then started to decrease gradually without changing ATRA dosage. Thrombocytosis may associate with cytokine.

Introduction

Acute promyelocytic leukemia (APL) is an aggressive type of acute myeloid leukemia (AML) associated with severe hemorrhagic syndromes and thrombotic problems [1]. This disorder is related to a reciprocal chromosomal translocation t(15;17)(q24;q21) involving retinoic acid receptor α (RARα) and its fusion partners including promyelocytic leukemia (PML) and promyelocytic leukemia zinc finger (PLZF), which leads to the *PML-RAR* chimeric gene formation [2]. This chromosomal translocation occurs between the long arm of chromosome 15, with a breakpoint at 15q24, and the long arm of chromosome 17, with a breakpoint at 17q21, which results in the lack of normal white and red blood cells and platelets in the body [1, 3]. There is an abnormal accumulations of immature blood-forming cells (promyelocytes) in the blood and bone marrow (BM). Unlike other forms of AML, APL is well treated by all-trans retinoic acid (ATRA; also known as tretinoin) therapy, as a criteria to distinguish this disorder from other forms of AML [4].

In most cases, ATRA therapy is well tolerated and its toxicity is modest. Hyperleukocytosis and the retinoic acid syndrome are two known complications. However, other side effects have been reported for APL including cheilosis, hypertriglyceridaemia, headache, bone pain, pseudotumour cerebri, skin dryness, and mucous membranes [5]. They are typically short-term and simply controlled by other therapeutic approaches [3, 6].

In this report, we reported a relatively uncommon side effect observed in a patient with APL during ATRA treatment.

Case history

The patient was a 28-year-old woman from Afghanistan without familial or personal history of blood problems or malignancies, history of any specific illness or medication. At the time of termination of pregnancy in Shahid Beheshti hospital, Kashan, Iran, she had pancytopenia (Table. 1). The patient was investigated to find the cause of pancytopenia. After termination of pregnancy, BM aspiration was carried out and its examination revealed abnormal accumulation of abnormal promyelocytic blasts. Promyelocytes included approximately 30 % of total BM cells (Figure. 1). Real time-polymerase chain reaction (RT-PCR) showed a PML-RARA fusion transcript. Low-risk APL (AML M3) was diagnosed according to the Sanz score which subdivides APL patients into three risk groups according to peripheral blood counts including: 1)

low-risk APL (platelet count >40×10^9/L and WBC [?]10x10^9/L); 2) intermediate-risk APL (platelet value [?]40x10^9/L and WBC count [?]10x10^9/L); 3) high-risk APL (WBC number >10x10^9/L) [7, 8]. Patient was initially treated with oral ATRA (45 mg/m2/day) and intravenous Arsenic Trioxide (ATO, 0.15 mg/kg/day) until complete remission achievement. On day 26 of ATRA therapy, the patient complained of blurred vision due to retinal bleeding and had decreased consciousness, headache and seizure. Magnetic resonance imaging (MRI) result showed intra-cerebral parenchymal bleeding in the frontal lobe. The patient had no history of any specific trauma or head injury. After seizure control, the patient was treated with supportive therapies such as intravenous levetiracetam (500 mg BD) and intravenous dexamethasone (8mg/12 hours). According to the neurosurgeon consultation, the patient did not need surgery. Furthermore, some laboratory tests were employed to exclude coagulation problems and find the cause of the bleeding. Similar to the results of at the initial diagnosis, no thrombotic and hemorrhagic problems were observed (Table. 2).

On day 26 to day 32 of treatment, laboratory blood tests indicated a notable thrombocytosis with the platelet counts of 590 x10^3/μl to 1280×10^3/μl (Figure. 2). No known causes of thrombocytosis such as infections, hemorrhagic disorders, haemolytic anemia, and iron deficiency were observed (9). Peripheral blood smear revealed a notable thrombocytosis and slight anemia (Figure. 3). Regarding the fact that the patient was asymptomatic, supportive care, ATRA, and ATO treatments were continued and ATRA dosage was not modified. Afterwards, platelet number spontaneously started to decrease on day 32 of treatment so that its number was 400×10^3/μl on day 42 (Figure. 2). On day 30 of ATRA therapy, BM examination showed a trilineal hematopoiesis with 1% of blasts and all criteria of morphological complete remission were observed (Figure. 4). Four consolidation courses of treatments were planned as previously described (10-13). After two consolidation courses of treatments, complete molecular remission was confirmed by the absence of PML-RARA fusion transcript using RT-PCR method.

Discussion

As reported by previous study [5, 14], thrombocytosis is considered as a rare side effect of treatment of APL patients with ATRA. The result of our patient revealed that ATRA treatment combined with ATO induced bone marrow megakaryocyte differentiation and platelet production. Several mechanisms have been proposed to the regulation of platelet production [15]. Thrombopoietin (TPO), a hormone usually produced by the liver and kidneys, is known as one of major mechanisms involved in the regulation of platelet production [16]. TPO stimulates the differentiation, proliferation, and maturation of megakaryocyte, a cell precursor of platelet production [17]. Another mechanism suggested to improve megakaryocytopoiesis is the release of immune agents such as IL-1, tumor necrosis factor (TNF), IL-2, IL-3, IL-11, IL-12, IL-6, and granulocyte macrophage-colony stimulating factor (GM-CSF) [14]. During ATRA therapy, APL cell under differentiation can produce IL-1β, IL-6, IL-8, and TNF-α. IL-1 and TNF-α may participate in enhancement of platelet counts through inducing IL-6 production [18]. Although it is suggested the correlations of these factors, especially IL-6, with the serum level of TPO [15], these associations are not well explained yet.

In a study on two APL patients who were treated with interferon alpha, Losada et al. reported that platelet number was increased more than $1000\times$ 10^9/L following treatment with ATRA [14]. Thrombocytosis was not accompanied by other clinical complications [14]. Subsequently, complete remission was obtained by ATRA therapy [14]. Furthermore, another study on a 20-year-old man with APL revealed a thrombocytosis on day 29 of ATRA treatment. ATRA dose was not modified and the increased number of platelet started to reduce gradually on day 33 of treatment. Finally, the patient reached to complete remission, without any complications associated with thrombocytosis [15]. The results of our case were consistent with previous studies showing thrombocytosis during ATRA therapy [11, 14, 15]. We observed an increased number of platelet (1280×10^3/μl) on day 32 of treatment. Thrombocytosis started to recover spontaneously on day 32 of ATRA, which is consistent with previous studies [15]. Our data were agreed with other reports pointing complete remission without any complications correlated to thrombocytosis can be achieved following ATRA treatment [12, 15].

Conclusion

These findings suggest that ATRA can induce severe thrombocytosis, as a potential side effect of treatment, in APL patients through stimulating the productions of different cytokines, especially IL-6, from APL cells under differentiation. However, further studies and more information are needed to confirm this conclusion and provide criteria for its management.

Conflict of interest

The authors report no conflict of interest.

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Authors' contributions

Maryam Habibi carried out some of the experiments and collected the laboratory findings. Reza Manouchehri Ardekani participated in the design of the experiments. Hossein Motedayyen drafted the manuscript and participated in the study design. All authors read and approved the final manuscript.

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Ethics statement

This study was approved by the Ethics Committee of Kashan University of Medical Science.

Data availability statement

All data generated or analyzed during this study are included in this published case report.

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Table. 1) Laboratory features of patient at the initial diagnosis

Table. 2) Laboratory findings of patient on day 26 of treatment

Figure legends:

Figure. 1: BM examination in a newly diagnosed APL patient (100×). BM examination revealed abnormal accumulations of promyelocytes (faggot cells) containing multiple Auer rods in the cytoplasm (arrow).

Figure 2: Platelet count curve from day 1 to day 42 of treatment with ATRA. Laboratory blood tests revealed the elevated numbers of platelets on day 26 to day 32 of treatment which this increase started to recover spontaneously on day 32 of treatment.

Figure 3: Peripheral blood smear of our patient (100×). Peripheral blood smear revealed a thrombocytosis and slight anemia.

Figure. 4: Bone marrow aspiration on day 30 of ATRA therapy in APL patient (100×). BM examination revealed the absence of promyelocytes with Auer rods which is a diagnostic criteria for complete remission of disease.