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Differentiation Syndrome Induced by Arsenic Trioxide when Receiving the Therapy of All-Trans Retinoic Acid/ Arsenic Trioxide Combination: A Case Report and Review of Literature

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Abstract

This report describes a case of Acute Promyelocytic Leukemia (APL) presented differentiation syndrome with typical symptoms (edema, acute renal failure and subcutaneous hemorrhage) after treatment with All-Trans Retinoic Acid (ATRA) and Arsenic Trioxide (ATO). We noticed that differentiation syndrome was caused by ATO. Symptoms of differentiation syndrome absolutely disappeared after stopping ATO and administering Dexamethasone. Then ATO was restarted and differentiation syndrome not presented again. Differentiation is a life threatening complication of therapy, which can be induced by All-Trans Retinoic Acid (ATRA) and Arsenic Trioxide (ATO). Nowadays, ATRA/ATO combination gradually becomes first-line chemotherapy of APL and we noticed that the death rate of DS induced by ATRA/ATO combination is lower than other chemotherapy. We review of some literatures and provide a strategy when DS presents.

Keywords: Acute promyelocytic leukemia; Arsenic trioxide; All-Trans Retinoic Acid; Differentiation Syndrome

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Abbreviations

APL: Acute Promyelocytic Leukemia; ATRA: All-Trans Retinoic Acid; ATO: Arsenic Trioxide; DS: Differentiation Syndrome; BM: Bone Marrow; FCM: Flow Cytometry; CR: Complete Remission; RAS: Retinoic Acid Syndrome

Introduction

Acute Promyelocytic Leukemia (APL) is a particular type of acute myelogenous leukemia almost characterized by the reciprocal translocations between the long arms of chromosomes 15 and 17 [t (15; 17)], called PML/RAR alpha. The PML/RAR alpha gene product acts as a transcription repressor, leading to the blocking of the differentiation of APL blasts at the stage of promyelocytes [1]. Pharmacological doses of All-Trans Retinoic Acid (ATRA) and Arsenic Trioxide (ATO) can reverse this blockage and induce disease remission. Despite the fact that ATRA and ATO were well tolerated in the majority of the APL patients, 2% to 31% of them develop a complication denominated Differentiation Syndrome (DS) [2]. DS is a life-threatening complication of therapy and is characterized by unexplained fever, hypotension, respiratory distress, pulmonary infiltrates, pleural effusions, pericardial effusions, acute renal failure, and hyperleukocytosis [3]. While differentiation syndrome induced by Arsenic Trioxide (ATO) is less reported, we report s case of an acute promyelocytic leukemia patient presented differentiation syndrome induced by ATO with typical symptoms (edema, subcutaneous hemorrhage and renal failure) after treatment with ATRA and ATO. Symptoms of differentiation syndrome absolutely disappeared after stopping ATO and continuing Dexamethasone. After several days of observation, ATO was restarted and differentiation syndrome not presented again. Besides, we summarized some literatures of differentiation syndrome.

Case Presentation

A 22-yr-old man was admitted to our hospital for the wound bleeding after tooth extraction. He

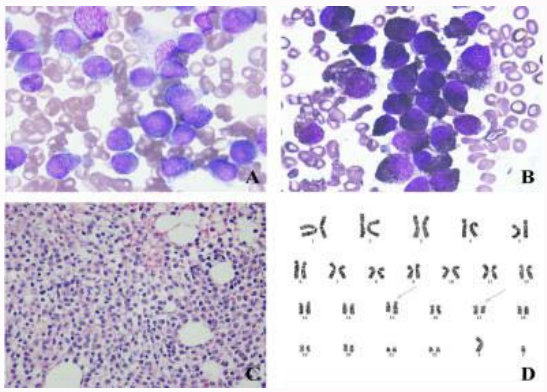

Figure 1: 1A) Bone marrow (BM) aspirate was hypercellularity with 62.5% progranulocyte, 2B) POX stained bone marrow aspirate was strongly positive, 2C) Bone marrow biopsy revealed increased blasts. 2D) Cytogenetics revealed t (15; 17) (q22; q21) translocation.

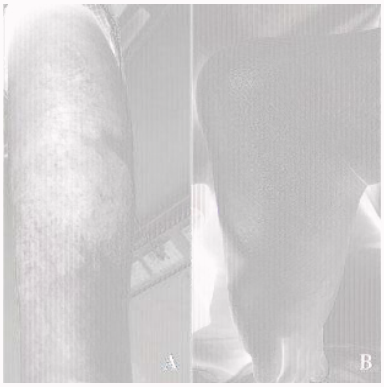

Figure 2: Skin manifestations of DS. 2A) Patients presented seriously whole-body edema, skin chap and (2B) extensive ecchymosis after treatment with ATRA and ATO.

had no personal or family history of previous medical problems, and he was taking no regular medication. At admission, full blood count revealed pancytopenia (hemoglobin 128.0 g/L, white cell count 2.41 × 10^9/L, neutrophils 0.75 × 10^9/L, and platelets 15 × 10^9/L). His alanine transaminase was 119 U/L, aspartate transaminase was 64 U/L, and his serum creatinine was 75 umol/L. His clotting profile revealed a raised prothrombin time and activated partial thromboplastin time with low fibrinogen. A Bone Marrow (BM) aspirate was hypercellularity with 62.5% progranulocyte, compatible with APL (Figure 1A). POX stained bone marrow aspirate was strongly positive (Figure 1B). Bone marrow biopsy revealed extremely active proliferation and increased blasts (Figure 1C). The chromosome of BM aspirate showed t (15; 17) (q22; q21) translocation (Figure 1D). Typical fusion gene of AML, PML/RAR alpha, was positive. Flow Cytometry (FCM) immunophenotyping showed that 48.4% of BM aspirated nucleated cells were abnormal myeloid blasts and likely were progranulocytes. ECG and chest radiograph were normal on admission. A diagnosis of APL was made.

The patient was received on ATRA (40 mg/day, divided into two doses) and ATO (10 mg/day). Also, the prophylactic antimicrobials were commenced. He was also treated supportively with packed red cells, platelets, fresh frozen plasma, and cryoprecipitate. After active treatment, the wound bled less. On day 8 of the cycle 1 of therapy, serum creatinine increased to 239 umol/L. In the next couple of days, the patient presented edema of limbs and eyelid, weight gain, pericardial effusions and subcutaneous hemorrhage. His skin manifestations were visible, such as edema, skin chap and ecchymosis (Figure 2). ATRA was subsequently discontinued due to the patient's deteriorating status. Because his constellation of symptoms and temporal relationship to his therapy was consistent with differentiation syndrome, Dexamethasone was administered as a resort effort at 10 mg IV twice daily. However, his symptoms continued to progress over the following days, and ATO was thought to be the reason that caused DS. Then we stopped ATO with Dexamethasone continuing. As we expected, within another five days Dexamethasone therapy, there was a remarkable improvement in his acute symptoms. His edema rapidly abated. His serum creatinine returned to baseline and pericardial effusions resolved. After several days of observation, ATRA and ATO were restarted at the same dose and no complication was presented differentiation syndrome not presented again. The case management process is summarized in (Table 1).

Discussion

APL was first described in 1957 by a Swedish author, Hillestad, and he noticed the disease accompanied a severe bleeding tendency. From 1973, Chemotherapy composed of an Anthracycline and cytosine arabinoside was the front-line treatment of APL, and the Complete Remission (CR) rates could reach 75% to 80% in newly diagnosed patients [4]. The treatment of APL has been revolutionized by the use of ATRA and ATO. In 1985, the effects of ATRA discovered in Shanghai, that opened a new page for treating APL. In 1988, Huang et al. reported that all of twenty-four patients with APL attained complete remission after treatment with all-trans retinoic acid [5]. In 1992, Frankel et al. noticed that 9 of 35 patients with APL who were treated with ATRA presented with a potentially lethal syndrome [3], then the retinoic acid syndrome started to be recognized around the world. Retinoic Acid Syndrome (RAS) is characterized by unexplained fever, weight gain, respiratory distress, interstitial

Table 1: The process of therapy.

Date	Management process	WBC × 10^9/L	Serum creatinine (umol/L)
d1	Supportive therapy	2.41	75
d2	Add ATRA	3.54	68
d5	Add ATO	13.37	123
d6	Add daunorubicin	24.79	181
d9	Stop daunorubicin	26.28	239
d17	Stop ATRA and add dexamethasone	8.46	192
d22	Stop ATO	1.25	136
d30	Restart ATRA and ATO	1.82	92

Abbreviations: d: day; WBC: White Blood Cell Count; ATRA: All-Trans Retinoic Acid; ATO: Arsenic Trioxide

Table 2: The incidence and death rate of DS induced by ATO or ATRA/ATO combination in clinical trials.

Author	Total no. of patients	Type of induction therapy	No. of DS patients (%)	Death resulting from DS, no. (%)
K Ohnishi et al. [7]	14	ATO	1(7)	0
Steven et al. [8]	40	ATO	10(25)	0
Ardeshir et al. [9]	197	ATO	NO	26(13)
Luis et al. [10]	26	ATO	8(31)	0
A. Mandegary et al. [11]	20	ATO	12(60)	2(10)
Estey et al. [12]	44	ATO+ATRA±GO	9(20)	0
Uwe et al. [13]	127	ATO+ATRA	21(16)	0
Harry et al. [14]	120	ATO+ATRA+CHT	17(14)	0
F. Lo-Coco et al. [15]	77	ATO+ATRA	15(19)	0
Hong-Hu Z et al. [16]	117	ATO+ATRA+CHT	29(25)	0
Hu J et al. [17]	85	ATO+ATRA	NO	1(1.2)

Abbreviations: DS: Differentiation Syndrome; ATRA: All-Trans Retinoic Acid; ATO: Arsenic Trioxide; GO: Gemtuzumab Ozogamycin; CHT: Chemotherapy; NO: Not Mentioned.

pulmonary infiltrates, pleural and pericardial effusion, dyspnea, hypotension and acute renal failure and at least three symptoms are needed [3]. Fortunately, RAS show high sensitivity to corticosteroid treatment.

At this time, ATO started been applied in APL and the first case of RAS-induced by arsenic trioxide was reported in 2000. We knew more about RAS, which could be induced by not only ATRA but also ATO, leading to differentiation syndrome more acceptable than RAS.

The incidence of DS has been reported to range from 2% to 31% in many clinical trials, which concluded from patients most treatment with ATRA and chemotherapy [2]. The incidence of DS caused by ATO has not been discussed. The incidence induced by ATO has reported to range from 7% to 60%, and the most frequent clinical manifestations are unexplained fever and dyspnea [7-11]. However, the most clinical signs of DS induced by ATRA are dyspnea, and pulmonary infiltrates [7-11]. Besides, the incidence of DS induced by ATRA/ATO combination is reported to range from 14% to 25% while the most frequent clinical manifestations are not mentioned [12-16]. From above, we can see the incidence of DS induced by ATO with a wider range, and it seems that the therapy of ATRA/ATO combination did not accompany with a higher incidence of DS. More important, there is only one death caused by severe DS induced by ATRA/ATO combination reported [17] (Table 2). All of these make us think there is any difference in the therapy of DS caused by ATRA/ATO combination with ATRA or ATO.

High-dose Dexamethasone, at a dose of 10mg, twice daily by intravenous injection, is recommended at the onset of the first symptoms, which could reduce the DS-related mortality to 1% or less in clinical trials [18]. Should we stop the drug or not is still on argument. European Leukemia Net hold the point that discontinuation of ATRA or ATO is indicated only in case of severe APL differentiation syndrome [19]. Chinese Society of Hematologist, Chinese Medical Doctor Association suggests that we should discontinue or reduce the dose of ATRA or ATO once DS is suspected [20]. However, DS induced by ATRA/ATO combination is different from DS induced by ATRA, and there is no clear suggestion of therapy of DS induced by ATRA/ATO combination.

In our case, the patient was started on ATRA (40 mg/day, divided into two doses) and ATO (10 mg/day) once the diagnosis was made. In the next couple of days, the patient presented edema, weight gain, pericardial effusions and subcutaneous hemorrhage with visible skin manifestations. ATRA was subsequently discontinued due to the diagnosis of DS and Dexamethasone was administered as a resort effort at 10 mg IV twice daily. However, his symptoms continued to progress over the following days, and ATO was thought to be the factor that caused DS. Then we stopped ATO with Dexamethasone continuing, and there was a remarkable improvement of his symptoms within the therapy of Dexamethasone.

Which one of ATRA or ATO plays a more prominent role is uncertain in DS induced by ATRA/ATO combination, and there is no research to verify that is needed or not to stop both of drugs when the diagnosis of DS was made. F. Lo-Coco et al. suggested stopping both agents at the earliest manifestations of suspected DS and administer dexamethasone until the disappearance of signs and symptoms for a minimum three days [16].

In our opinion, we could stop one agent of ATRA and ATO and administer Dexamethasone (at 10 mg IV twice daily) when differentiation syndrome is not severe. And stop both agents of ATRA and ATO only when symptoms continue to progress. Then add one of them after symptoms of differentiation syndrome absolutely subside. If no complications present, we should restarted the other agent after one week.

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