İstanbul Üniversitesi Sağlık Bilimleri Enstitüsü Sağlık Bilimlerinde İleri Araştırmalar Dergisi
Istanbul University Institute of Health Sciences Journal of Advanced Research in Health Sciences

Sağlık Bilimlerinde İleri Araştırmalar Dergisi 2021, Cilt 4, Sayı 2
DOI: 10.26650/JARHS2021-826059 Case Report/ Olgu Sunumu

Intracardiac Thrombus Associated with All-Trans-Retinoic Acid Treatment in a Child with Acute Promyelocytic Leukemia

Akut Promyelositik Lösemili Çocuk Hastada All-Trans-Retinoik Asit Tedavisiyle İlişkili İntrakardiyak Tromboz

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Submitted/Geliş tarihi: 15.11.2020
Accepted/Kabul Tarihi: 06.05.2021

Citation/Atıf: Canbolat Ayhan A, Baysal A, Tosun O. Intracardiac thrombus associated with all-trans-retinoic acid treatment in a child with acute promyelocytic leukemia. Sağlık Bilimlerinde İleri Araştırmalar Dergisi 2021; 4(2): 81-86. https://doi.org/10.26650/JARHS2021-826059

ABSTRACT

In acute promyelocytic leukemia (APL) potentially fatal coagulopathy and hemorrhages remain major causes of induction failure. Serious thrombotic events are frequently reported at the diagnosis or following remission induction therapy with all-trans-retinoic acid (ATRA), which is a key point in treatment of APL. On the other hand, isolated right ventricular (RV) thrombus is a life-threatening condition and in cancer patients it has been rarely reported. In this report, we have described a very rare a case of ATRA-related isolated right-sided intracardiac thrombus in a nine-year-old child with APL that developed after achievement of complete remission, during the 4th course of ATRA, which is an unexpected period for ATRA-related thrombotic events. We aimed to emphasize the importance of side effects of ATRA and increase awareness against such life-threatening complications. Thrombosis mustn't be expected only during differentiation syndrome; it should be kept in mind in every phase of treatment with ATRA.

Keywords: Acute promyelocytic leukemia, All-trans-retinoic acid, Intracardiac thrombus

ÖZ

Ölümcül koagulopatiler ve hemorajiler akut promiyelositik lösemide (APL) indüksiyon tedavisine yanıt alınamamasının temel sebeplerini oluşturmaktadır. Ağır trombotik olaylar genellikle tanı sırasında ya da tedavinin kilit noktasını oluşturan all-trans-retinoik asit (ATRA) ile remisyon indüksiyon tedavisine başlanmasından hemen sonra gelişir. Diğer yandan izole sağ ventrikül içi tromboz hayatı tehdit edici bir patoloji olup kanser hastalarında nadir olarak saptanmıştır. Bu çalışmada remisyonda iken sağ ventriküler kardiyak trombüs gelişen dokuz yaşındaki APL olgusu nadir görülmesi nedeniyle sunulmuştur. ATRA'nın yan etkilerinin öneminin gösterilmesi, ölümcül olabilen komplikasyonların vurgulanması amaçlanmıştır. Trombozun sadece diferansiyasyon sendromunu sırasında değil tedavinin her döneminde gelişebileceği akılda tutulmalıdır.

Anahtar Kelimeler: Akut promiyelositik lösemi, All-Trans-Retinoik Asit, İntrakardiyak tromboz

INTRODUCTION

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia (AML), which is characterized by a chromosomal abnormality involving translocation between chromosomes 15 and 17 (1). APL is uncommon in children less than 10 years of age. The complete remission rate is 90-95% (2). ATRA, which is a derivative of vitamin A, is a key point in the therapy of APL and it is a molecular targeted therapy, which induces differentiation of APL cells. ATRA is used as adjunctive therapy in combination with chemotherapy (1). Potentially fatal coagulopathy and hemorrhages remain major causes of induction failure in patients diagnosed with APL. While bleeding is one of the usual manifestations of APL, thromboembolic events have been less frequently reported. In APL, thrombosis typically develops after initiation of ATRA. ATRA has a procoagulant effect due to increased production of cytokines and also due to expression of adhesive molecules on both promyelocytes and endothelium (3). On the other hand, isolated RV thrombus is a potentially life-threatening condition and in cancer patients it has been rarely reported (4).

Herein, we have reported a case of right-sided intracardiac thrombus related to ATRA during the 4th course of ATRA in a child diagnosed with APL who was receiving chemotherapy in combination with ATRA.

CASE PRESENTATION

Our patient was a 9-year-old boy diagnosed with APL. Bone marrow aspiration was positive for translocation t(15;17). Induction chemotherapy was started with ATRA (25 mg/m2/day p.o) as a single agent following an AML-BFM 2013 chemotherapy regimen. ATRA was planned as 14-day cycles concomitant with chemotherapy. A transthoracic echocardiography was performed before induction therapy, which showed normal findings. He was monitored for differentiation syndrome and disseminated intravascular coagulation (DIC). A port catheter was inserted in the subclavian vein. The catheter tip was in the distal superior vena cava. He did not develop differentiation syndrome. Bone marrow puncture was performed prior to the second induction therapy. It demonstrated remission with <5% blasts. He completed the second course of chemotherapy. Before the third course of chemotherapy, we performed a bone marrow aspiration and it demonstrated complete remission; molecular cytogenetics was negative for t(15;17). Control echocardiographies and cardiac evaluations were performed before the start of the second and third courses and revealed normal findings. Before the start of consolidation chemotherapy (the 4th chemotherapy course), screening echocardiography was performed again. He was receiving his fourth 14-day-ATRA course and he was on the 13th day of the course. This time the echocardiography showed two masses, which were characterized by hyperechogenicity attached to the intraventricular septum of the right ventricle (RV) suggesting thrombus (Figure 1). One of the masses was close to the moderator band (7x8 mm) and the other (5x5 mm) was close to the tricuspid valve. Cardiac systolic functions were preserved; ejection fraction (EF) was 65%. Cardiac MRI confirmed the presence of these masses, suggesting thrombus. The patient had no complaint. He was in good physical condition. His pulse rate and blood pressure were in normal limits. He was afebrile and he had no signs or symptoms of infection. His complete blood count, baseline biochemistry, C-reactive protein (CRP) and urinalysis were normal. Prothrombin time (PT) was 13.4 s, INR: 1.04, PT: 94%, activated partial thromboplastin time (APTT) was 27.3 s, fibrinogen was 196 mg/dl and D-dimer level was 1 mg/L. Chest X-Ray was normal. The port catheter tip was in the distal superior vena cava. Lower limb venous color doppler ultrasonography did not reveal signs of deep or superficial thrombosis. Inherited and acquired thrombophilia screening tests, which were available on those days at our center, were performed and the results were as follows: Protein C:92%, protein S:76%, antithrombin III: 104%, prothrombin G20210A: homozygous normal, MTHFR: homozygous normal, factor XIII: homozygous normal, homocysteine: 7.94 umol/L, anticardiolipin IgG:2.1 u/ml, anticardiolipin IGM:2 u/ml, antip-

hospholipid IgG:3.1 u/ml, antiphospholipid IgM:1 u/ml, factor VIII:104%, factor IX: 115%, factor XI:128%, factor XII: 102%. Probability of the development of thrombosis due to ATRA was likely, so a diagnosis of isolated right ventricle thrombosis in the setting of ATRA was made. ATRA was stopped and chemotherapy was postponed. The patient was immediately started on enoxaparin (100 IU/kg every 12 h) subcutaneously (SC). One week after initiation of enoxaparin, a control echocardiogram was performed and it showed no significant changes. Fourteen days after initiation of enoxaparin, control echocardiogram showed slight reduction in the dimensions of the masses and enoxaparin was continued. Unfortunately, on the 32nd day of enoxaparin, our patient developed fever and his blood counts declined progressively. Laboratory data showed deep neutropenia, thrombocytopenia, and severe elevation of C-reactive protein (CRP). PT was 18.8 s, INR was 1.62, PT was 51%, APTT was 34.1 s, and fibrinogen level was 217 mg/dl. He was treated as having febrile neutropenia. Despite the intensive supportive treatment he developed sepsis and died one week thereafter.

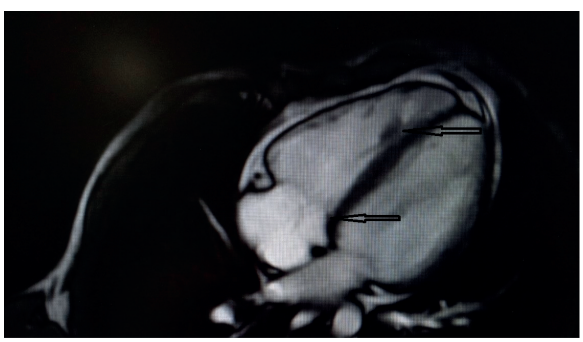

Figure 1. MRI scan showing thrombosis in the Right Ventricle

DISCUSSION

Thrombotic complications such as disseminated intravascular coagulation are more frequent in APL than in other types of acute leukemias. A large range of incidence of thrombosis in APL has been reported, changing from 2% to 19% (5-7). In the study conducted by Breccia, the incidence of thrombosis was reported as 8.8% and the sites of thrombosis were deep vein thrombosis, subendocardiac ischemia and intraventricular thrombosis (8).

It has been reported previously that more than 80% of thrombotic events occurred before or during induction therapy (9). APL cells express tissue factor (TF) and cancer procoagulant (CP), which are known as tumor-associated procoagulants (2,3). Although ATRA is generally well tolerated, some patients may develop ATRA-related complications ranging from mild to moderate. Retinoic acid syndrome (RAS) is a well-known potentially life-threatening side effect of ATRA. Cardiovascular complications, such as isolated myocarditis, arrhythmia, bradycardia, and atrioventricular blockage as a result of RAS related to ATRA have been reported rarely (10,11). These complications are mostly seen during induction therapy with ATRA. Pancreatitis, intracranial hypertension, dry skin, fatigue, bone and joint pain, increase of liver enzymes, hypertriglyceridaemia, and perimyocarditis are other reported adverse events (10,12-13). Recent reports show that the incidence of thrombotic complications is also rising (14-16). A pulmonary embolism case in remission of APL has been reported (15). It was shown that retinoids induce increased production of plasminogen activator inhibitors such as PAI-1 and PAI-2 which may lead to APL-related thrombosis (17). ATRA therapy and PAI-1 gene 4G/4G polymorphism might lead to APL-related thrombosis. (3,17). The proposed pathophysiology involves tissue infiltration of APL cells and production of chemokines. Treatment with ATRA results in the rapid resolution of APL-associated coagulopathy (2). During the first 7-14 days of treatment with ATRA, normalization of markers of clotting-activation and also markers of activation of hyperfibrinolysis are expected (2). It has been demonstrated that in patients treated with ATRA, low-level elevation of activation markers of clotting can persist and ATRA can predispose to a low-level prothrombotic state (18). In our case it was difficult for us to differentiate whether the development of this thrombus was related to ATRA or that the thrombus developed after achievement of complete remission. Unfortunately, our case report had some limitations, such as

being unable to complete all thrombophilia tests. He was receiving only ATRA at the time of diagnosis of the thrombosis. Initial thrombophilia tests performed at diagnosis ruled out other causes of thrombosis. The occurrence of thrombus was three months after initiation of ATRA, therefore we couldn't say that it was related to the differentiation syndrome and our patient did not develop differentiation syndrome. Furthermore, differentiation syndrome is unlikely after remission is achieved. Probability of the presence of thrombus due to initial diagnosis of APL was unlikely because an echocardiography was performed before the start of ATRA and chemotherapy and it was normal. On the other hand, isolated RV thrombus is a potentially life- threatening condition and in cancer patients it has been rarely reported (4). There are no specific guidelines for the management of intracardiac thrombus, but we think that early discontinuation of ATRA and postponement of chemotherapy seem likely to prevent the progression of thrombus. Unfortunately, we were unable to evaluate the efficiency of enoxaparin in our patient.

To conclude, we want to point out that thrombosis should be kept in mind at every step of treatment of APL. It must not be expected only during the presentation of the disease or after initiation of ATRA. Further study is warranted for treatment of intracardiac thrombus in cancer patients.

Peer Review: Externally peer-reviewed.

Hakem Değerlendirmesi: Dış bağımsız.

Informed Consent: Written consent was obtained from the participants

Bilgilendirilmiş Onam: Katılımcılardan bilgilendirilmiş onam alınmıştır.

Author Contributions: Conception/Design of Study- A.C.A., A.B. Ö.T.; Drafting Manuscript- A.C.A., A.B. Ö.T.; Final Approval and Accountability- A.C.A., A.B., Ö.T.

Çalışma Konsepti/Tasarım- A.C.A., A.B. Ö.T.; Yazı Taslağı- A.C.A., A.B. Ö.T.; Son Onay ve Sorumluluk- A.C.A., A.B., Ö.T.

Conflict of Interest: Authors declared no conflict of interest.

Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir

Financial Disclosure: Authors declared no financial support.

Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

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