Introduction

Acute promyelocytic leukemia (APL) is a subtype of acute myeloid leukemia. It has distinct morphology, clinical presentation, and cytogenetics. It often presents with pancytopenia, coagulopathy, and bleeding manifestation that requires urgent diagnosis and treatment. APL is the result of a balanced translocation between chromosomes 15 and 17 \( [t(15;17)] \).\(^1,2\)

Translocation \( (15;17) \) leads to promyelocytic leukemia and retinoic receptor-\(\alpha\) fusion gene \( (PML–RAR\alpha) \). This oncoprotein subsequently blocks the differentiation of myeloid cells at the promyelocytic stage. All-\(trans\) retinoic acid (ATRA) induces a structural change of \( PML–RAR\alpha \) and induces promyelocytes’ differentiation into mature myeloid cells.\(^1\) Combination of ATRA with anthracycline leads to complete remission rate of 90%–95% in APL patients.\(^1,3\)

A 45-year-old female, a new case of acute promyelocytic leukemia (APL), received induction chemotherapy containing all-\(trans\) retinoic acid (ATRA) and idarubicin. On the sixth day of therapy, she developed sinus bradycardia and differentiation syndrome (DS). Electrolytes and cardiac imaging were normal. The patient achieved normal sinus rhythm after ATRA was withheld, and DS was treated.

Keywords: Acute Promyelocytic Leukemia, all-\(trans\) retinoic acid, bradycardia, differentiation syndrome (DS), idarubicin, \( PML–RAR\alpha \)

Case Report

A 45-year-old female with no underlying comorbidity such as cardiovascular disease or hypertension got admitted with per recta l bleeding, epistaxis, and upper limb ecchymosis. Laboratory evaluation showed white blood cells (WBC) 3,200/mm\(^3\), promyelocyte 66%, hemoglobin (Hb) 6.5 g/dL, platelet 57,000/mm\(^3\), prothrombin time 18.5 s, international normalized ratio 1.52, and partial thromboplastin time (PTT) 29 s. Her fibrinogen was 140 mg/dL, total bilirubin 0.73 mg/dL, aspartate aminotransferase 40 U/L, alanine transferase 45 U/L, and serum creatinine 0.9 mg/dL. Bone marrow aspirate was consistent with APL, and cytogenetics confirmed \( t(15;17) \). Chest X-ray and Non contrast computed tomography (NCCT) head were normal.

Treatment of APL with ATRA results in differentiation syndrome (DS) in up to 50% of patients.\(^4\) DS is characterized by shortness of breath, hypoxia, fever, weight gain, hemoptysis, pulmonary infiltrates, pleural, and pericardial effusion.\(^5,6\) DS is treated with dexamethasone, and ATRA should be discontinued.\(^5,6\) Common side effects of ATRA are headache, dry skin, xerostomia, bone pain, and nausea.\(^7\) Cardiovascular manifestations, such as bradycardia, have rarely been reported.
Electrocardiogram (ECG) on admission was normal [Figure 1]. ATRA at a dose of 45 mg/m²/day was administered in two divided doses. On the sixth day of ATRA administration, WBC progressively increased to 12,300/mm³. She had shortness of breath, weight gain of 6 kg, and developed fever. Oxygen saturation had dropped to 90% on room air, and chest X-ray showed bilateral pulmonary infiltrate. She had sinus bradycardia at 40 beats/min [Figure 2]. These symptoms are closely associated with ATRA administration; a diagnosis of DS was made. ATRA was stopped and intravenous dexamethasone was given 10 mg twice daily till improvement of DS. On day 6, 8, 10, and 12, she received idarubicin 12 mg/m². By day 9, symptoms of DS had fully resolved. On day 10, her ECG was in normal sinus rhythm [Figure 3]. Her WBC count was 5,500/mm³. She was given half-dose ATRA on day 11 and on the subsequent day, full dose of ATRA was administered. Patient was in molecular remission on day 40 of induction and in regular follow-up for consolidation therapy, and no incidence of bradycardia was found.

**Discussion**

Sinus bradycardia may be due to sinoatrial node dysfunction. Causes include sick sinus syndrome, ischemic heart disease, cardiomyopathy, hyperkalemia, hypothyroidism or hyperthyroidism, and medications. In our case, there was no single underlying comorbid condition that can lead to sinus bradycardia, except that the patient was receiving ATRA and idarubicin induction for APL. Idarubicin usually causes tachycardia. It causes cardiotoxicity in a dose-dependent manner. The Naranjo adverse drug reaction probability scale was 7 for ATRA. The onset of bradycardia during induction of APL is from day 4 to 25 in reported cases.

Maruhashi et al[8] used ATRA induction, which developed sinus bradycardia on day 4 in their case.

Yamauchi et al,[9] in their case, developed complete atrioventricular (AV) block on day 25 of ATRA and mitoxantrone induction. Patient needed temporary pacemaker and was in normal sinus rhythm on day 15 after withholding ATRA. In the case reported by Dhar et al,[10] the patient developed second-degree AV block on day 9 after ATRA induction due to DS and was treated with dexamethasone. Patient was in sinus rhythm after resolution of DS.

McGregor et al,[11] in their case, used ATRA and idarubicin for induction. Patient developed junctional bradycardia on day 5 of DS. Patient was in sinus rhythm after treatment of DS. Karakatsanis et al[12] used ATRA and idarubicin for induction. On day 8, patient developed sinus bradycardia, but no DS during treatment.

Shih and Wu,[13] in their case, used ATRA induction, and on day 15, patient developed complete AV block. They used temporary pacemaker, and after stopping ATRA, patient was in sinus rhythm on day 4. Chen et al,[14] in their case, used ATRA, idarubicin, and Arsenic Trioxide (ATO) induction. On day 11,
patient developed complete heart block; ATRA was stopped and temporary pacemaker was used to treat AV block. Heart rate partially recovered after 3 days. After restarting ATRA, patient developed DS and heart block. After treatment of DS, patient was in sinus rhythm.

In our case, patient received induction with ATRA and idarubicin. Patient developed sinus bradycardia and DS on day 6. ATRA was stopped and DS treated. On day 9, patient’s symptoms resolved. on day 11, patient was rechallenged with ATRA half dose. There was no bradycardia. On next day, patient received full dose of ATRA. Kang and Leaf demonstrated that ATRA significantly lowered the heart rate and reduced the incidence and severity of ventricular tachyarrhythmia induced by isoproterenol in rats. ATRA acts on membrane ion channels and may result in conduction disturbance of the AV node. Another possible mechanism of ATRA-related arrhythmia is leukemic cell infiltration in the myocardium. On autopsy, showed leukemic cell infiltration in the His bundle of his and led to second degree heart block in acute myeloid leukemia patient.

Primary care physician to whom patients visits first for any drug adverse reaction should be aware of such a rare side effect of ATRA.

**Conclusion**

ATRA may cause conduction dysfunction-related arrhythmia. Close monitoring of vital signs and performing ECG are recommended during ATRA-based induction therapy.

**Key points**

1. ATRA can cause conduction defect during induction in APL.
2. Monitoring by ECG should be done while using ATRA in APL induction.
3. ECG should be done before starting ATRA.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

---

**References**

1. Wang ZY, Chen Z. Acute promyelocytic leukemia: From highly fatal to highly curable. Blood 2008;112:2505-15.
2. Network NCC. Acute Myeloid Leukemia. Version 1, 2016. Available from: https://www.nccn.org/professionals/physician_gls/PDF/aml.pdf.
3. Sanz MA, Lo-Coco F. Modern approaches to treating acute promyelocytic leukemia. J Clin Oncol 2011;29:495-503.
4. Iland HJ, Bradstock K, Supple SG, Catalano A, Collins M, Hertzberg M, et al. All-trans-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4). Blood 2012;120:1570-80.
5. Rogers JE, Yang D. Differentiation syndrome in patients with acute promyelocytic leukemia. J Oncol Pharm Pract 2012;18:109-14.
6. Sanz MA, Montesinos P. How we prevent and treat differentiation syndrome in patients with acute promyelocytic leukemia. Blood 2014;123:2777-82.
7. DiPiro J, Talbert RL, Yee G, Wells B, Posey LM. Acute leukaemia’s. In: Poon BB, Seung AH, editors. Pharmacotherapy: A Pathophysiologic Approach. 9th ed. New York, NY, USA, McGraw-Hill Medical; 2014.
8. Maruhashi K, Wada H, Taniguchi M, Koizumi S. Sinus bradyarrhythmia during administration of all-trans retinoic acid in a patient with acute promyelocytic leukemia. Rinsho Ketsueki 1996;37:443-7.
9. Yamauchi T, Arai H, Taga M, Amaya N, Lee JD, Ueda T. Adams-stokes attack due to complete atrioventricular block in a patient with acute promyelocytic leukemia during remission induction therapy using all-trans retinoic acid. Rinsho Ketsueki 2005;46:206-10.
10. Dhar AK, Barman PK. Retinoic acid syndrome-cardiac complication. J Assoc Physicians India 2012;60:63-5.
11. McGregor A, Hurst E, Lord S, Jones G. Bradycardia following retinoic acid differentiation syndrome in a patient with acute promyelocytic leukaemia. BMJ Case Rep 2012;bcr0220125848.
12. Karakatsanis S, Vardaka M, Giannoulia P, Apostolidis J, Delimpasi S. Bradycardia during induction therapy with all-trans retinoic acid (ATRA). J BUON 2014;19:315.
13. Shih CH, Wu HB. All-trans retinoic acid-induced, life-threatening complete atrioventricular block. J Chin Med Assoc 2015;78:316-9.
14. Chen P-Z, Wu Y-J, Wu C-C, Wang Y-W. Bradycardia during Induction therapy with all-trans retinoic acid in patients with acute promyelocytic leukaemia: Case report and literature review. Case Rep Hematol 2018;2018:1-6.
15. Kang JX, Leaf A. Protective effects of All-trans-retinoic acid against cardiac arrhythmias induced by isoproterenol, lysophosphatidylcholine or ischemia and reperfusion. J Cardiovasc Pharmacol 1995;26:943-8.
16. Ferla V, Sciure M, Gianelli U, Baldini L, Fracchiolla NS. Multiple adverse drug reactions during all-trans retinoic acid treatment for acute promyelocytic leukaemia: Differentiation syndrome, bradycardia, intestinal necrosis. Explor Target Antitumor Ther 2020;1:109-16.
17. Hatake K, Saito K, Saga T, Akashi N, Doishita K. A case of acute myelogenous leukemia with advanced atrioventricular block and pericardial effusion caused by leukemic cell infiltration. Jpn J Med 1982;21:115-9.