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Case Report

All-*trans* retinoic acid-induced, life-threatening complete atrioventricular block

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Abstract

We report a case of complete atrioventricular block (CAVB) with ventricular asystole and recurrent AVBs due to all-*trans* retinoic acid (ATRA). A 57-year-old man with acute promyelocytic leukemia was undergoing induction therapy with ATRA and developed episodic seizures with altered consciousness on the 14th day and then CAVB followed by cardiac arrest on the 15th day. Although he initially recovered after resuscitation, he suffered from recurrent CAVB, which persisted for 3 days despite immediate ATRA discontinuation. He then received ATRA retreatment with reduction of dosage, but a high-degree AVB recurred on the 5th day. After discontinuation of ATRA therapy, the patient recovered 3 days later without any cardiovascular event during follow-up. The serial electrocardiogram changes suggested an infra-Hisian block with possible ATRA dose-response relationship. To our knowledge, this is the first established case of ATRA-induced CAVB in the literature. We suggest clinical alertness for this life-threatening complication.

Keywords: acute promyelocytic leukemia; all-*trans* retinoic acid; arrhythmia; complete atrioventricular block

1. Introduction

Acute promyelocytic leukemia (APL) comprises 10–15% of acute myelocytic leukemia and is characterized by marked proliferation of leukemic promyelocytes in the bone marrow, life-threatening coagulopathy, and a specific reciprocal translocation of t(15;17). APL used to be a highly lethal subtype of acute leukemia, with up to a 47% early hemorrhagic death rate before or during induction chemotherapy and a 2-year survival of 30–50%.[1] However, the advent of all-trans retinoic acid (ATRA) in the 1980s revolutionized the therapy of APL, leading to dramatic decreases in early hemorrhagic death, to 5–10%, and overall survival, to 85–90%.[2]

Herein, we report a case of APL developing a very rare but life-threatening CAVB during ATRA therapy. The causal role of ATRA was established by rechallenge, and the serial electrocardiogram (EKG) changes suggested a possible dose-response relationship.

2. Case report

A 57-year-old man with type II diabetes mellitus was admitted due to fever and leukopenia. The blood routine revealed leukopenia (1.6×10^9/L), anemia (10 g/dL), and thrombocytopenia (24×10^9/L) with immature white cells. The bone marrow study suspected APL, but septicemia due to *Acinetobacter baumannii* had to be treated during the initial course with intravenous ciprofloxacin that was later changed to cefepime due to persistent fever.

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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After bone marrow cytogenetics confirmed a three-loci translocation of APL [46, XY, t(15;22;17)(q24;q13;q21)], ATRA (45 mg/m^2/d) was given orally. The patient experienced an ATRA-related mild headache and bone pain, but mucositis became aggravated later and the dosage was reduced to 75% from the 5th day of therapy. Molecular study reported a long-type PML/RARa fusion mRNA 2 weeks later.

On the 13th day of ATRA therapy, an episode of transient aphasia and general paresis occurred, but urgent computed tomography of the brain showed negative results. On the following day, the patient then developed episodic generalized convulsions with delirium. Laboratory surveys revealed no significant abnormalities. Valproic acid was given under suspicion of myoclonic seizure to relieve the symptoms.

On the 15th day of ATRA therapy, the patient experienced another episode of fluctuating consciousness disturbance in the morning. Bedside EKG monitoring showed a first-degree AVB with a regular heartbeat of 94 beats/min (Fig. 1A), and later, the EKG showed CAVB with ventricular escape (Fig. 1B). In the afternoon, a complete loss of consciousness suddenly occurred after yawning. The patient was found unresponsive and without spontaneous breathing or heartbeat. A shot of epinephrine was given immediately followed by cardiopulmonary resuscitation. The ventricular rate resumed after treatment, but severe bradycardia recurred due to CAVB 2 hours later, necessitating a second resuscitation.

We stopped the ATRA therapy and administered temporary cardiac pacing for the patient; an echocardiogram did not demonstrate any structural defect of the heart, but varying degrees of heart blocks persisted for 3 days (Fig. 2A–C) before conversion to sinus rhythm on the 20th day. Due to suspicion of ATRA as the inciting agent, we reduced its dose during retreatment and placed the patient under close EKG telemetric monitoring. However, on the 5th day of treatment, high-degree AVB with 2:1 AV conduction (Fig. 2D) recurred without significant clinical symptoms. The drug was discontinued immediately, and the AVB disappeared gradually over 3 days without further recurrence. Throughout the episodes, there was no evidence of retinoic acid syndrome (RAS), such as the characteristic features of fever, respiratory distress, pulmonary infiltration, pleural or pericardial effusion, or weight gain, nor did the patient receive any arrhythmogenic or node-blocking medication.

3. Discussion

The retinoid acids are derived from vitamin A, and bind to the nuclear retinoic acid receptors (RARs). The RARs then undergo heterodimerization and bind to DNA to facilitate gene transcription and control post-transcriptional expression. The t(15;17) translocation of APL fuses the *PML* (promyelocytic leukemia) gene to the gene RARα, and the resultant fusion gene *PML-RARa* produces the PML/RARα oncoprotein, which forms homodimer and competitively blocks granulocytic differentiation.[2] The pharmacological dose of ATRA leads to dissociation of the nuclear corepressor, which presumably facilitates APL maturation.[3]

ATRA has been a relatively safe drug, with few serious adverse effects as compared to conventional chemotherapy. The more common side effects, including headache, dry

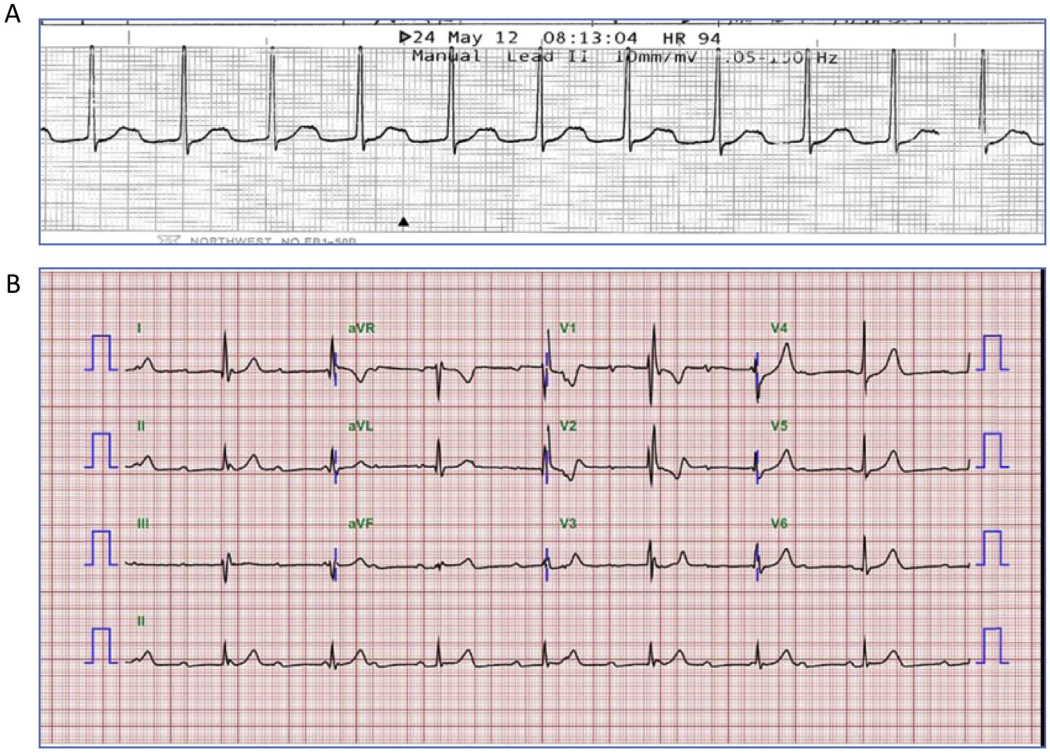

Fig. 1. Serial electrocardiogram changes before and after the life-threatening complete atrioventricular block (AVB): (A) 7 hours before cardiac arrest: first-degree AVB (P-R interval = 360 ms); (B) 2 hours before cardiac arrest: complete AVB with ventricular escape (15th day of all-*trans* retinoic acid).