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CASE REPORT

Cardiac stunning as a manifestation of ATRA differentiation syndrome in acute promyelocytic leukemia

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Introduction

Acute promyelocytic leukemia (APL) is a specific type of acute myelogenous leukemia characterized by the reciprocal translocations between the long arms of chromosomes 15 and 17 [*t*(15;17)] leading to the fusion of the retinoic acid receptor and the promyelocytic leukemia (PML) genes, called *PML/RARalpha*. The *PML/RARalpha* gene product acts as a transcription repressor, resulting in the blocking of the differentiation of APL blasts at the stage of promyelocytes. Pharmacological doses of all-*trans* retinoic acid (ATRA) reverse this blockage and induce disease remission. However, although ATRA is well tolerated in the majority of the APL patients treated with ATRA and idarubicin regimen (AIDA), approximately one quarter of them develop a complication denominated ATRA differentiation syndrome (DS), formerly known as retinoic acid syndrome [1–3]. The onset of DS ranges from 2 to 21 days (median of 10 days) after initiating ATRA therapy. The full development of DS is characterized by unexplained fever, weight gain, edema, interstitial pulmonary infiltrates with dyspnea, pleural and pericardial effusions, episodic hypotension, and acute renal failure. The most frequent manifestations are respiratory distress and fever, affecting more than 80% of DS patients. Acute myocardial ischemia is not commonly observed in DS. As far as we know, there is only one case report describing this complication [4]. Through early diagnosis, DS responds well to the administration of dexamethasone, with decrease in mortality from 30% to less than 10% in the patients suffering from it. The pathogenesis of this complication is not completely clarified, but increased expression of adhesion molecules on blasts and on endothelial cells and the release of inflammatory cytokines may be the main explanation [5].

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Case presentation

A 76-year-old female patient was diagnosed with APL. At admission, laboratory tests showed hemoglobin concentration of 11.0 g/dL, WBC count of 1.5×10^9/L, with 2% of blasts, and platelet count of 146×10^9/L. The bone marrow aspirate showed homogeneous infiltrate of promyelocytes (some with Auer rods), compatible with APL. The LDH level was 268 U/L (normal range 200–480 U/L). The coagulation tests showed APTT of 79 s (ratio of 2.63), INR of 1.32, and fibrinogen of 165 mg/dL. The PML/RARalpha rearrangement was demonstrated in bone marrow by reverse transcriptase-polymerase chain reaction studies (RT–PCR). The patient did not present symptoms or signs of infection.

Treatment with ATRA (45 mg/m^2/day), associated with cytarabine (20 mg/m^2/day), was immediately started. Anthracycline was not administered because of the patient's age. After 3 days of therapy, coagulation tests became (and remained) normal throughout the disease course. Fourteen days after the beginning of ATRA treatment, the patient was admitted to the emergency ward with severe central chest pain, which had begun a few hours before, and hypotension. She had never presented chest

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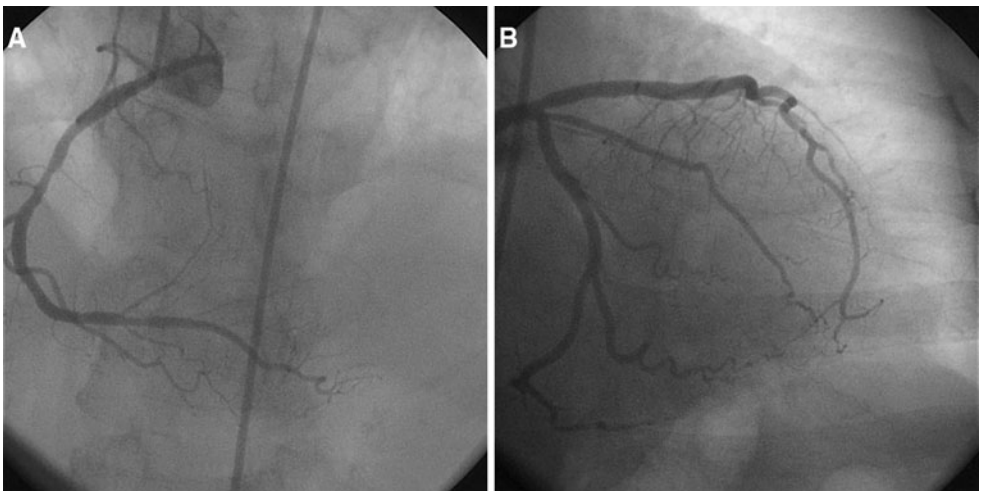

Fig. 1 **a** Right coronary angiogram in left anterior oblique view; **b** Left coronary angiogram in right anterior oblique caudal view

pain before and had no specific risk factors for ischemic heart disease, such as diabetes, obesity, hypertension, dyslipidemia, or history of smoking. The patient was submitted annually to cardiologic evaluation and had no identified problem.

At admission, the patient had a troponin of 4.0 mg/dL ($N < 0.06$ mg/dL) and a CKMB of 65 U/L ($N < 25$ U/L). Electrocardiogram showed normal pattern (no ST segment changes and or inverted T-waves).

That same day the patient underwent a cardiac catheterization and a Doppler echocardiography. The angiography showed an insignificant constriction in the right coronary that could not be attributed to the myocardial ischemia (Fig. 1a). The other coronaries had no obstructions (Fig. 1b). The echocardiography showed a reduced left ventricular (LV) contractility, with ejection fraction of 0.49 ($N > 0.56$), and global systolic left ventricular dysfunction with hypocontractility in the anteroseptal segment. The hemoglobin concentration was 10.1 g/dL, WBC cell count was 9.9 $\times$ 10^9/L, and platelet count was 39 $\times$ 10^9/L. The patient received nitrates for a few days and dexametasone (20 mg/day, divided in two doses) for 8 days. Due to the thrombocytopenia, the patient did not receive platelet antiaggregants. The following day the patient was asymptomatic and blood pressure returned to the normal limits. Two days afterward, the troponin and CKMB levels were normal and the patient was discharged from hospital. After 5 days, ATRA was restarted at the same dose and maintained for 2 more weeks. Two months later, the echocardiogram was repeated and showed a normal ejection fraction and no segmental hypocontractility. After achieving hematological remission, the patient received conventional maintenance therapy with 6 mercaptopurine and ATRA for two and a half years. The patient is now in hematological and molecular remission. She has never had another episode of myocardial ischemia.

Conclusions

In the last 20 years, the current protocols for the treatment of APL include various combinations of ATRA and chemotherapy. This approach has contributed to reduce the early mortality and to increase remission rates [6, 7]. Nonetheless, ATRA therapy is not free from side effects, although they are generally mild. Here, we report a case of acute myocardial ischemia associated with the administration of ATRA. The patient had no other risk factors for vascular disease and the coronary angiography showed no flow-limiting stenosis.

We have found in literature only one case report that associating DS with myocardial infarction [4]. Montesinos et al. studied 739 patients with APL treated with ATRA and observed that approximately 25% of patients developed DS, half of them in a severe form. A multivariate analysis indicated that WBC count was higher than 5 $\times$ 10^9/L and abnormal creatinine level correlated with an increased risk of developing severe DS [3]. The patient in this report had WBC count of 1.5 $\times$ 10^9/L and normal serum creatinine, suggesting a low risk of severe DS. Thrombosis was described in patients with APL, and it is believed to be more common than suggested by previous publications [8–10]. The use of ATRA could exacerbate the procoagulant state of APL and increase the incidence of thrombosis, which is estimated in approximately 5%, according to two recent studies [3, 11]. This case could be considered an episode of transitory ischemia that impaired the myocardial function temporarily, as 2 months later the myocardial function was completely normal, without any sign of sequela, as defined by an echocardiogram evaluation. We do not believe in a direct effect of ATRA on myocardium, as the reintroduction of this drug did not cause recurrence of cardiac failure nor takotsubo cardiomyopathy (also known as the transient left ventricular

apical ballooning syndrome); as the clinical picture was not preceded by any emotional or physical event, there was no alteration of ST segment and the echocardiography showed hypocontractility of anteroseptal, not apical segment [12]. Moreover, cardiac biomarkers returned to normal levels rapidly, instead of the slow fall commonly observed in this syndrome. For these reasons, we believe that clinical picture herein described could be defined as a myocardial stunning [13]. This entity is an acknowledged clinical condition that occurs whenever ischemia is followed by reperfusion. In this case, the reperfusion occurred spontaneously or, more probably, due to the administration of nitrates and corticosteroids. We believe this patient had a cardiac stunning secondary to differentiation syndrome initiated by ATRA therapy, a complex syndrome not fully understood, but with a central participation of activated blasts in the process of differentiation and overexpression of some adhesion molecules [5]. This is the most plausible hypothesis as the obstruction observed in the right coronary is not considered sufficient to provoke obstruction of blood flow. Besides, the myocardium affected was the anteroseptal segment that is irrigated by the left anterior descending coronary (which did not present any obstruction to blood flow) and not by the right coronary, a finding that suggested a 'non-vascular' obstruction to blood flow. We believe this is the first report of a cardiac stunning case secondary to DS.

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