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CARDIAC TAMPONADE AND CARDIOGENIC SHOCK AS A MANIFESTATION OF ALL-TRANS RETINOIC ACID SYNDROME: AN ASSOCIATION NOT PREVIOUSLY REPORTED

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ABSTRACT

Since the discovery of the differentiating activity of all-trans retinoic acid (ATRA) in acute promyelocytic leukemia (APL), the treatment of this disease has greatly improved. Currently, the combination of ATRA and chemotherapy is considered the best treatment for patients with APL. This approach has consistently extended the remission rate and disease-free survival of APL patients with low mortality. Among ATRA's adverse effects, the retinoic acid syndrome is the most important. It consists of fever, dyspnea, weight gain, pulmonary infiltrates and pleural and cardiac effusions. Other findings occasionally described are lower extremities edema and leukocytosis. We report a case of an retinoic acid syndrome associated with cardiac tamponade due to massive pericardial effusion. This adverse effect, not previously reported, was successfully treated by performing pericardiocentesis followed by the administration of dexamethasone.

Key words: acute promyelocytic leukemia, ATRA syndrome, cardiac tamponade

Acute promyelocytic leukemia (APL) is a distinctive subtype of acute myeloid leukemia (AML) distinguished from all other AMLs by characteristic blast morphology, life-threatening coagulopathy, and specific rearrangement of the chimeric PML/RARα gene resulting from the balanced translocation t(15;17), which confers a special sensitivity to all-trans retinoic acid (ATRA).[1] Since the discovery of the differentiating activity of ATRA in APL blasts, the treatment of APL has improved considerably.[2] Current treatment protocols, including various combinations of ATRA and chemotherapy, result in better control of the APL-associated coagulopathy, strikingly high remission rates and improved disease-free survival.[3-7] Nonetheless, ATRA therapy is not free from side effects, although they are generally mild (xerosis, bone pain, cheilitis, headache, hypertriglyceridemia). However, a more severe complication, retinoic acid syndrome, has been observed in up to 26% of the patients treated with ATRA alone.[8] Although the incidence of this complication in patients treated with ATRA and chemotherapy may be lower, definitive data are still lacking. Retinoic acid syndrome consists of progressive, fever, dyspnea, weight gain, pulmonary infiltrates and pleural and cardiac effusions. The syndrome may be associated with other findings such as edema in lower limbs and leukocytosis.[8]

We report a case of retinoic acid syndrome associated with cardiac tamponade due to massive pericardial effusion. This adverse effect, not previously reported, was successfully treated by performing pericardiocentesis followed by the administration of dexamethasone.

Case Report

A 19-year-old male with a history of postraumatic splenectomy was admitted to the hospital because of fever, hematuria and ecchymoses on the lower limbs. At admission laboratory tests showed a hemoglobin of 3.6 g/dL, a WBC count of 20.2×10^9/L, with 95% atypical promyelocytes, and a platelet count of 41×10^9/L. The LDH level was 1,495 U/L (normal range 225-500 U/L). The Quick index 42%, fibrinogen 90 mg/dL and the APTT 41 seconds (normal range 17-25 seconds). A bone marrow aspirate showed a homogeneous infiltrate of hypogranular promyelocytes with bilobed nucleus and Auer rods, compatible with a variant form of APL. The translocation t(15;17) and the PML/RARα rearrangement were demonstrated in bone marrow by cytogenetic and reverse transcriptase-polymerase chain reaction (RT-PCR) studies respectively. Treatment with ATRA (45 mg/m^2/d), daunorubicin (60 mg/m^2/d x 3 days) and cytarabine (200 mg/m^2/d x 7 days) was immediately started. However, despite chemotherapy, a progressive increase of the leukocyte count was observed, reaching 20×10^9/L on day 5 of ATRA therapy. Concomitantly, the patient presented dys-

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pnea and progressive hypoxemia (pO2, 59 mmHg) associated with precordial pain, silenced cardiac tones, tachycardia, hypotension and a low urinary output. Pulmonary arterial pressure was 35/24 mmHg, pulmonary capillary wedge pressure 22 mmHg and central venous pressure 18 mmHg. Radiographs of the chest showed bibasal infiltrates. Echocardiography detected a large pericardial effusion causing cardiac tamponade. The patient was admitted to the critical care unit 20 hours after the onset of symptoms, and pericardiocentesis was then performed. Macroscopically, the pleural fluid obtained was clear. At cytological examination no cells were detected, and the biochemichal analysis showed the following results: glucose 117 mg/dL, proteins 6 g/dL and LDH 824 U/L (protein and LDH levels in plasma were 6.6 g/dL and 325 U/L respectively).

At this time, ATRA was discontinued and therapy with dexamethasone was started (10 mg/12h intravenously over three days). The clinical status of the patient improved progressively and he was discharged in complete remission two weeks later. Currently, fourteen months after diagnosis, the patient maintains normal cardiac function and is in continuous complete remission.

Discussion

Nowadays, the combination of ATRA and chemotherapy is considered the best treatment for patients with APL.[3-7] This approach has consistently improved the remission rate and disease-free survival of APL patients with low mortality.[3-7] Among ATRA's adverse effects, retinoic acid syndrome is the one most frequently reported, with an estimated incidence of 26%.[8]

Though not well defined, the physiopathology of this syndrome seems to be related to ATRA-induced cytokine secretion by APL blasts. These cytokines may increase the number of circulating blasts, their adherence and activation, which, in turn, would lead to the distress symptoms and the pericardial and pleural effusions seen in individuals with this complication.[9] To prevent the development of this syndrome, simultaneous treatment with ATRA and chemotherapy is generally recommended when the leukocyte count at diagnosis exceeds 6×10^9/L. However, this approach is not always effective and, as occurred in our patient, the retinoic acid syndrome may develop. In those patients with low leukocyte numbers it is mandatory to perform complete blood counts daily once ATRA has been started. Additional chemotherapy could be administered if an increase in leukocytes is observed. Once established, this syndrome is difficult to manage, though early administration of dexamethasone (10 mg/12 hours) has achieved the best results.[8,9]

Although the appearance of a pericardial effusion in patients treated with ATRA is a known and common feature of retinoic acid syndrome, we wish to draw attention of the development of cardiac tamponade with secondary cardiogenic shock as a severe and not previously reported manifestation of this syndrome.

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