Retinoic Acid Syndrome - Cardiac Complication

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Abstract

Retinoic acid syndrome is a novel complication of therapy with all-trans retinoic acid (ATRA) in patients with acute promyelocytic leukemia (APML). Primarily the syndrome consists of fever and respiratory distress. Additional features include weight gain, oedema over lower extremities, pleural or pericardial effusion and hypotension. We report electrophysiological changes in a 16 year old patient with acute promyelocytic leukemia following treatment with ATRA. Such an unusual complication is a rarity and to the best of our knowledge has not been previously reported.

Case Report

A 16-year-old female was admitted in a service cancer hospital with complaints of bleeding gums, fever and generalized weakness. On clinical examination the patient was febrile, anemic and there were purpuric spots on the body. Laboratory investigations showed Hb of 5gm/dl, leucopenia (Total count 2x10^9/L) and thrombocytopenia( 20x10^9/L). Bone marrow aspiration morphology according to FAB criteria was suggestive of APML (Figure 1). Bone marrow cytogenetics showed a balanced translocation between chromosome 15 and 17 (t 15:17) which confirmed diagnosis of acute promyelocytic leukemia (Figure 2).

Coagulogram showed disseminated intravascular coagulation (D.I.C.) indicated by raised PT, PTTK level and decreased serum fibrinogen (150mgm/dl). Other investigation including ECG and x-ray chest were normal at the time of admission.

Patient was started on ATRA (45mgm/m²) and over the next seven days, the coagulation profile improved. By day 8 of treatment, the leukocyte count had escalated to 15x10^9/L, and abnormal promyelocytes showed differentiation into phenotypically mature myeloid cells. Patient developed dyspnoea and generalized bone pains and by day 9, she developed irregular cardiac rhythm. ECG showed Wenckebach phenomenon with progressive increase in PR interval till a P wave dropped (Figure 3). The cycle repeated itself with 6: 5 and 5: 4 conduction patterns with progressive increase in PR interval till a P wave dropped. The QRS duration was normal. X-ray chest showed right sided pleural effusion (Figure 4) and echocardiography showed mild pericardial effusion (Figure 5).

The patient was treated with glucocorticoids (dexamethasone 10mg IV twice a day) and ATRA was continued. The leucocytosis was controlled and symptomatically the patient improved and achieved normal sinus rhythm. Steroids were discontinued (after the clinical improvement) when the total counts reduced to 5 x10^9/ L. Patient achieved complete remission on day 21 of treatment with ATRA. Repeat serial ECG’s and X-ray chest were normal and repeat echocardiography showed no evidence of pericardial effusion. The patient continues to be in complete remission after consolidation therapy with anthracyclines followed by maintenance therapy. The disease free interval has been 26 months.
Discussion

Retinoic acid syndrome and hyperleucocytosis has been well described in acute promyelocytic leukemia on treatment with ATRA. The mechanism of action of ATRA in APML is through induction of apoptosis. Drug induced release of vasoactive cytokines from differentiating leukemic cells would explain fever, weight gain and episodic hypotension. Organ infiltration by leukemic cells is quite common. The probable mechanism of retinoic acid syndrome in our case may be leucocytosis leading to occlusion of small blood vessels and migration of maturing cells into the lungs and pericardium and myocardium. Hyperleucocytosis is one of the fatal complications of ATRA. It has been previously treated with leukapheresis, aggressive combination chemotherapy and even by discontinuation of ATRA. Our case was treated with steroids and did not require discontinuation of ATRA. The resolution of manifestations of retinoic acid syndrome, was accompanied by simultaneous improvement in conduction disturbances and pleuroparicardial effusion without additional therapy. The mechanism of the block is not described and remains speculative.

Normal QRS Wenckebach phenomenon indicate that the site of block appears to be AV node itself. The cause of AV node involvement may be migration of maturing cells or oedema due to release of cytokines which resolved with steroids. This puts forth a strong case for including electrophysiological changes on ECG as an additional feature of retinoic acid syndrome and cautions to users of this drug against potentially serious bradyarrhythmias due to retinoic acid syndrome in case preexisting bradyarrhythmias are present or concomitant bradyarrhythmic drugs are used.

References