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I A. Burney
Aga Khan University

M U. Islam
Aga Khan University

M Khursheed
Aga Khan University

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Retinoic Acid Syndrome: A Potentially Fatal Side Effect of Retinoic Acid Therapy

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Ikram A. Burney (Departments of Medicine, The Aga Khan University Hospital, Karachi.)

M. Umar Islam (Radiology, The Aga Khan University Hospital, Karachi.)

M. Khursheed (Pathology, The Aga Khan University Hospital, Karachi.)

The management of acute promyelocytic leukemia (APL) has changed over the past few years¹⁻². The discovery of specific molecular abnormality (PML/RAR-cz gene product) has raised considerable interest in the management of the disorder with All trans- retinoic acid (ATRA)³⁻⁵. The compound is now being increasingly used for the remission-induction in APL. However, the drug is not free of side effects. We report a potentially fatal side effect of the drug in two patients.

Case 1

A 23 year old lady presented with pancytopenia and was diagnosed to have APL. The patient also had right basal consolidation at presentation. She was started on ATRA, at a dose 45 mg/m² in two divided doses. It was planned that ATRA would be administered for a total of 90 days. She also received antibiotic therapy consisting of Cloxacillin, Amikacin and Ceftazidime. On the 5th day of therapy, the patient became acutely dyspnoeic and restless. On examination, the respiratory rate was 32/mm., BP 140/80mm Hg, Pulse 160/min, temperature 37°C. Auscultation of the chest revealed decreased breath sounds on the left side. The chest x-ray showed infiltrates throughout the right lung with complete opacification of the left hemithorax. Arterial blood gasses showed severe arterial hypoxemia. Because of the continuously decreasing O₂ saturation, the patient was intubated and ventilated. A chest tube was passed on the left side which drained 650 ml of hemorrhagic fluid. A subsequent CBC revealed a total leucocyte count of 28,400/uL. Dexamethasone 10 mg b.i.d. parenterally, was initiated immediately. Subsequently, Cytosine Arabinoside ma dose of 100 mg/m² was administered for five days and Daunorubicin in adose of 45 mg/m² for two days. Over the next several days, clinical as well as the radiological picture improved. About 3 weeks after the acute episode, the chest x-ray showed complete resolution of bilateral infiltrates and pleural effusion. The chest tube was removed and the patient was subsequently extubated. The patient returned to the ward, where a bone marrow aspirate showed her to be in complete remission.

Case 2

A 37 year old lady presented with history of menorrhagia and easy bruisability and was found to be pancytopenic. Her full blood count revealed a hemoglobin of 8.4 g/dl total leucocyte count 0.9x10⁹/L and platelet count 18x10⁹/L. The liver and renal function tests were within nonnal limits. The bone marrow aspirate acute promyelocytic leukemia according to the FAB criteria. The patient was started on remission - induction treatment with ATRA 45 mg/m² daily into two divided doses. On the 6th day of treatment, the white cell count increased to 19,000/uL and remained at this level over the next couple of days. The patient became febrile and developed a hematoma on the right upper arm, which was painful, warm, tender and resulted in limitation of movements at the elbow joint. Antibiotics were started but the fever continued. Blood cultures remained negative. On the 8th day of treatment with ATRA, she developed another hematoma in her right calf followed by one in left calf. Peripheral blood smear showed persistent leukocytosis with left shifted neutrophils. The fever continued to spike despite the use of antibiotics. On the 21st day of treatment with ATRA, the patient suddenly became dyspnoeic and tachypnoeic. The respiratory rate was found to be 42/min. Auscultation of the chest revealed bilateral crepitations and there was severe hypoxemia. Chest x-ray showed bilateral fluffy infiltrates.

Dexamethasone 10 mg was injected immediately and an endotracheal tube passed. She also developed oliguria and systemic hypotension and eventually succumbed to persistent severe hypoxemia.

Discussion

Acute promyelocytic leukemia (APL) comprises 10% of all cases of acute myeloid leukemia⁶. The disease is characterized by increased bleeding tendency, primarily due to disseminated intravascular coagulation (DIC), which may occur in upto 80% cases of APL⁷. Although chemotherapy is highly effective in inducing remissions, it may also exacerbate the DIC by rapidly releasing cytoplasmic granules from the malignant promyelocytes⁸. The incidence of fatal hemorrhage during the course of initial treatment is more than 30 percent⁸. The identification of a non- random chromosomal abnormality resolves within the first 48 hours of the treatment. The treatment is generally well tolerated, except for modest degree of dry skin, cheilosis, nasal stuffiness and itching¹³. However, in about a quarter of patients, the side effects may assume life threatening proportions. These side effects have been reported to occur between the second day and the third week of the treatment and consist of fever, respiratory distress, radiographic pulmonary infiltrates and pleural and pericardial effusions. Collectively, these have been termed together as the retinoic acid syndrome^{9,10,14}. The pathophysiology of the syndrome, is unclear, but clinically it resembles the capillary leak syndrome observed in patients treated with cytokines^{10,15}. It is postulated that the syndrome may be a consequence of the fusion transcript activity on the intracellular adhesion molecules¹⁰. As the leukemic cells differentiate, they migrate to the pulmonary capillary bed, express the adhesion molecules, liberate vasoactive cytokines, which result in capillary leak and consequent clinical abnormalities. Similar changes occur in the capillary bed of kidney, liver, skin and lymph nodes^{10,16}. Multi-organ failure ensues and if the syndrome is not recognized early and treated promptly, it may be rapidly fatal. The syndrome is difficult to manage once established; however, dexamethasone 10mg i/v every 12 hours has been shown to halt the progress of rapidly evolving cellular events in a number of patients¹⁴. The patients may require drainage of pleural effusion and mechanical ventilation may be necessary till the resolution of symptoms as was the case in our first patient.

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References

1. Huang, M, Yu-Chen, Y., Shu-Rong, C. et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. *Blood*, 1988;72:567-572.
2. Warrell, R.P., Frankel, S.R., Miller, W.H. et al. Differentiation therapy for acute promyelocytic leukemia with tretinoin (all-trans-retinoic acid). *N. Engl. J. Med.*, 1991;324:1385-87.
3. de-The, H., Chomienne, C., Lannote, M. et al. The t(15; 17) translocation of acute promyelocytic leukemia fuses the retinoic acid receptor gene to a novel transcribed locus. *Nature*, 1990;347:558-561.
4. Avvisati, O., Petti, M.C. and Mandelli, F. What is the best treatment for acute promyelocytic leukemia? *Lymphoma*, 1993;2:29-35.
5. Frankel, S.R., Eardley, A., Heller, O. et al. All trans retinoic acid for acute promyelocytic leukemia. Results of the New York Study. *Ann. Intern. Med.*, 1994; 120:278-286.

6. Stone, R.M. and Mayer, R.J. The unique aspects of acute promyelocytic leukemia. *Clin. Oncol.*, 1990;8:1913-1921.
7. Tallman, M.S. and Kwaan, H.C. Reassessing the hemostatic disorder associated with acute promyelocytic leukemia. *Blood*, 1992;79:543- 553.
8. Rodghiero, F, Avvisati, O., Caataman, G. et al. Early deaths and anti-hemorrhagic treatments in acute promyelocytic leukemia: A GIMEMA retrospective study in 268 consecutive patients. *Blood*, 1990;75:2112-2117.
9. Rowley, J.D., Golomb, H.M. and Dougherty, C. 15/17 Translocation: A consistent chromosomal change in acute promyelocytic leukemia. *Lancet*, 1977;1:549-550.
10. Warrell, R.P., de-The, H., Wang, I.Y. et al. Acute promyelocytic leukemia. *N. Engl. J. Med.*, 1993;329:177-189.
11. Huang, ME., Ye, Y.C., Chen, S.R. et al. Use of all trans retinoic acid in the treatment of acute promyelocytic leukemia. *Blood*, 1988;72:567-572.
12. Warrell, R.P., Frankel, SR. Miller, W.H. et al. Differentiation therapy of acute promyelocytic leukemia with tretinoin (all-trans-retinoic acid). *N. Engl. J. Med.*, 1991 ;324:1385-1393.
13. Eardley, A.M., Heller, O. and Warrell, R.P. Morbidity and costs of remission induction therapy with all-trans retinoic acid compared with standard chemotherapy in acute promyelocytic leukemia. *Leukemia*, 1994;8 :934-939.
14. Frankel, SR., Eardley, A., Lauwers, G. et al. The 'retinoic acid syndrome' in acute promyelocytic leukemia. *Ann. Intern. Med.*, 1992;117:292-296.
15. Margolin, K.A., Rayner, A.A., Hawkins, M.J. et al. Interleukin-2 and lymphokine-activated killer cell therapy of solid tumours: Analysis of toxicity and management guidelines. *J. Clin. Oncol.*, 1989;7:486-498.
16. Grignani, F., Fagioli, M., Atcalay, M. et al. Acute promyelocytic leukemia: From genetics to treatment. *Blood*, 1994;83: 10-25.