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ALL-*TRANS* RETINOIC ACID INDUCED THROMBOCYTOSIS IN A PATIENT WITH ACUTE PROMYELOCYTIC LEUKAEMIA

We read with interest the paper by Losada *et al* (1996) reporting two cases of severe thrombocytosis occurring in patients with acute promyelocytic leukaemia (APL) during all-*trans* retinoic acid (ATRA) treatment. Toxicities of ATRA are multiple; they include dryness of the skin and mucous membranes, cheilosis, headache, hypertriglyceridaemia, bone pain, and pseudotumour cerebri. Two life-threatening side-effects have been reported: hyperleucocytosis $>20\times10^9$/l occurring in 25% of patients, and retinoic acid syndrome characterized by fever, respiratory distress, heart failure, pulmonary infiltrates, pleuropericardial effusions and oedema. We present the case of a patient with a similar history of severe thrombocytosis occurring during treatment with ATRA for APL.

In December 1995 a 49-year-old patient presented with a 2-month history of progressive asthenia followed by spontaneous cutaneous haemorrhages. Laboratory blood tests at presentation were: WBC $1{\cdot}8\times10^9$/l (PMN 18%, lymphocytes 34%, monocytes 7%, eosinophils 3%, metamyelocytes 11%, myelocytes 16%, promyelocytes 8%, blasts 3%, erythroblasts 3%), haemoglobin 7·6 g/dl, platelets 16×10^9/l. Disseminated intravascular coagulation was present. APL was diagnosed by bone marrow examination which showed 23·7% of abnormal promyelocytic blasts. Cytogenetic studies disclosed the presence of the chromosomal translocation t(15;17). The patient was given ATRA 45 mg/m^2/d orally, combined with idarubicin every 2 d for 8 d according to the GIMEMA-AIEOP 'AIDA' protocol (Avvisati *et al*, 1996). On day 7 the patient complained of headache and blurred vision. An eye fundus disclosed a bilateral papiloedema without retinal haemorrhage. As the brain computed tomography was normal, the diagnosis of pseudotumour cerebri was considered to be very probable and treatment with ATRA was interrupted. After recovery of normal vision and disappearance of headaches, ATRA was re-administered on day 12 without further side-effect. On day 29, BM examination was normal but all criteria of complete remission were not obtained in the peripheral blood (WBC count $6{\cdot}6\times10^9$/l, platelets 179×10^9/l, but Hb 8·2 g/dl). It was planned according to the protocol to continue ATRA alone until day 60. On day 42, laboratory blood tests disclosed a significant thrombocytosis with a platelet count of 1071×10^9/l. No obvious cause of thrombocytosis, for example no signs of infection, or chronic inflammatory syndrome, or haemorrhage, or haemolytic anaemia could be found (Williams, 1995). The only other medication, in addition to ATRA, administered at that time was insulin. ATRA was thought to be a potential cause of the thrombocytosis and was interrupted. The platelet count decreased to 960×10^9/l after 2 d and reached normal values on day 56. Complete remission was obtained at day 60. Three consolidation courses were then completed. As no minimal residual disease at the molecular level could be demonstrated, the patient was randomized to sequential maintenance treatment with 6MP, MTX and ATRA.

During maintenance treatment with ATRA (45 mg/m^2/d for 15 d), no recurrence of the thrombocytosis was observed. 14 months after the beginning of therapy, the patient is perfectly well.

The close temporal correlation between the administration of ATRA and the occurrence of the thrombocytosis and its prompt disappearance after the interruption of therapy suggest that the side-effect was due to ATRA.

As reported by Losada *et al* (1996), severe thrombocytosis is a potential side-effect of ATRA in APL.

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