Acute leukaemia during azathioprine therapy

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Summary

Various tumours, in particular lymphomas, have been reported in association with azathioprine treatment, both after renal transplantation and in other conditions. A case is reported here of acute myeloid leukaemia associated with azathioprine therapy for rheumatoid arthritis, and this is now the third case reported in the world literature of leukaemia arising during azathioprine therapy for a non-malignant condition.

Case report

In April 1974 a 73-year-old woman presented with increasing weakness, shortness of breath, haemoptysis and recent rectal and vaginal bleeding. She had suffered from rheumatoid arthritis for over 30 years, but for the last 15 years it had been difficult to control, with considerable pain and stiffness in her knees, shoulders and hands, requiring systemic steroids and/or ACTH. More recently she was taking chlorpropamide for diabetes. In January 1971 she was admitted to hospital for the third time within a year for an exacerbation of her arthritis and was started on azathioprine 100 mg daily. In November 1972 this was reduced to 50 mg, on which she continued until her admission in April 1974. Monthly blood counts remained normal, the last being in February 1974.

Examination

She was pyrexial (38.5°C) with fresh bruising on her arms and a haematoma at the site of a recent intramuscular injection on one buttock. She was in atrial fibrillation at a ventricular rate of 130, and there were signs of consolidation at the base of the right lung. There was no lymphadenopathy or splenomegaly.

Investigations

Initial investigations showed: Hb - 9.9 g/dl;

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WBC - $19.9 \times 10^9/l$. Polymorphs 5%; metamyelocytes 12%; lymphocytes 4%; myelocytes 45%; stab cells 2%; promyelocytes 22%; blast cells 10%. Platelets $30 \times 10^9/l$. Sternal marrow—hypercellular marrow easily aspirated. Hyperplasia of myeloid precursors. Abnormal binucleate myelocytes and promyelocytes. Promyelocytes 18%; blast cells 10%. Cytochemical stains confirmed acute myeloid leukaemia.

Treatment

She was treated initially with ampicillin and cloxacillin and, when her pneumonia was controlled, with cytosine arabinoside 200 mg i.v. daily and thioguanine 30 mg orally three times daily for two 5-day courses with a 5-day interval between. She failed to respond to treatment and died 15 days after admission. Permission for a post-mortem examination was not obtained.

Discussion

The association between non-Hodgkin lymphomas and azathioprine is well documented and occurs at a frequency greater than that of chance (Doll and Kinlen, 1970). Such lymphomas show a curious predilection for the brain. Most reported lymphomas have occurred in patients who have received renal homograft transplants but there have been some case reports of lymphomas arising during azathioprine treatment for other conditions (Sharpstone, Ogg and Cameron, 1969; Worledge *et al.*, 1968). There have also been reports of other malignant tumours arising during azathioprine therapy including pancreatic sarcoma and adenocarcinoma of the lung (McAdam, Paulus and Peter, 1974), but these single instances may have been fortuitous associations. Squamous cell carcinoma of the skin, however, is a relatively frequent accompaniment of azathioprine treatment following renal transplantation. Acute leukaemia had not been reported until a recent paper by Silvergied and Schrier (1974) describing two cases of acute myeloid leukaemia

arising during azathioprine treatment. One was a young man with chronic active hepatitis and the other a man who had received a renal transplant.

It has been suggested that lymphoproliferative disorders are more common in patients with autoimmune diseases including rheumatoid arthritis irrespective of treatment (Lea, 1964; Miller, 1967) but, in a review of the evidence, Oleinck (1967) concludes this to be unproved. A case similar to the present one was reported by Maldonado *et al.* (1968) in which a 7-year-old boy with pyoderma gangrenosum developed acute leukaemia after 12 months' treatment with mercaptopurine, a drug closely related to azathioprine. However, in that case there was evidence of plasma cell dyscrasia with disordered immunoglobulins during the initial illness of pyoderma gangrenosum, and the terminal illness was thought to be a plasma cell leukaemia. It seems unlikely, therefore, that the mercaptopurine was causal.

There are theoretical grounds for expecting malignant growths to arise during immunosuppression (Keast, 1970; Woodruff, 1969) and lymphomas have been produced by azathioprine experimentally in mice (Casey, 1968). Although the association between azathioprine and acute myeloid leukaemia may be fortuitous, this is now the third case described. As there is currently an enormous increase in the use of immunosuppressive agents, particularly for non-malignant conditions, physicians should be aware of this possible grave complication.

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