None of them had a history suggestive of tropical spastic paraparesis, the other known syndrome associated with HTLV-1 infection. Our patient was a second generation immigrant from south China. She had never travelled to HTLV-1 endemic areas, but had received a blood transfusion for post-partum haemorrhage during delivery of her first child.

Comment

HTLV-1 infections have not been widely documented in east Asia outside of Japan and Taiwan. The seroepidemiological pattern of this infection in South East Asia has not been well studied. A recent serological survey of 9689 healthy blood donors and pregnant women in Singapore showed an incidence of 0·03% (unpublished data). This is close to the 0·025% seroprevalence documented in blood donors in the United States.[4]

The fact that both vertical and horizontal transmission of this infection can readily occur is well illustrated by this case. This ease of transmission is of concern, especially when pockets of HTLV-1 infection have been documented in unusual areas.[5] At the least, seroepidemiological trends must be monitored to ensure that the problem does not take on greater proportions.

The low seroprevalence of HTLV-1 in non-endemic areas is likely to preclude cost-effective screening of blood donors. Patients with mature T-cell lymphoid malignancies, however, should be screened for infection. Contact tracing after identification of the index case is likely to be fruitful. The detection of infected patients, together with counselling on the modes of transmission, may help to prevent further transmission and protect national blood resources.

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Treatment of acute myeloid leukaemia in a renal allograft recipient: Implications of cyclosporin immunosuppressive treatment

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Abstract

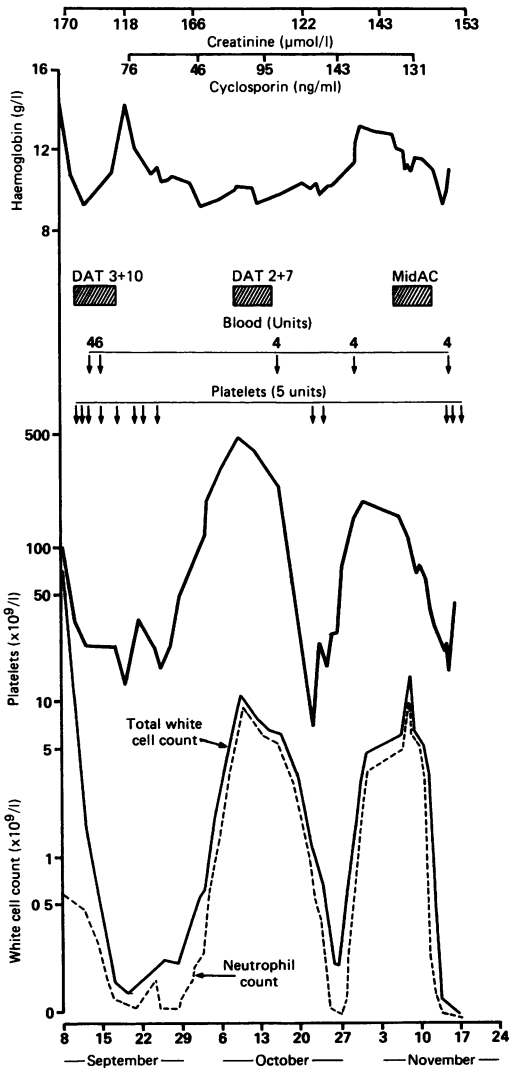
The clinical effects of cyclosporin were evaluated during cytotoxic treatment in a 61 year old man with acute myeloid leukaemia. He had required a renal transplant 18 months before presenting with acute myeloid leukaemia (FAB subtype M4). He had received cyclosporin 3·5–4·0 mg/kg daily to maintain a plasma cyclosporin concentration of 75–150 ng/ml. Cyclosporin was continued during induction chemotherapy with daunorubicin, cytarabine, and 6-thioguanine (DAT). He had fever and oropharyngeal candidiasis that was unresponsive to anti-bacterial drugs but responsive to systemic amphotericin. Bone marrow examination 14 days after chemotherapy showed complete haematological remission. Subsequently he tolerated consolidation treatment with DAT with no serious complications. Unfortunately he developed fatal septicaemia following a second consolidation with mitozantrone and cytarabine.

Inhibition of P-glycoprotein activity by cyclosporin may not significantly increase the toxicity of aggressive chemotherapeutic regimens, and as benefit may be achieved by this approach further clinical evaluation is justified.

In the management of malignant disease resistance to cytotoxic drugs often makes treatment unsuccessful. Interest has developed in studying the possible benefits of inhibiting the activity of P-glycoprotein to circumvent cytotoxic drug resistance.[1] P-glycoprotein is a 170 kilodalton transmembrane glycoprotein which acts as an energy dependent pump, causing active efflux of structurally hetero-

geneous substances, including daunorubicin and vincristine, from cells. It is encoded by the MDR-1 gene. The multidrug resistant phenotype is characterised by overexpression of P-glycoprotein. This can be recognised in several malignancies including acute myeloid leukaemia (AML).[2] In AML it occurs most frequently in relapse following previous heavy cytotoxic exposure. Excessive expression results in inadequate intracellular concentrations of cytotoxic drugs such as daunorubicin, and consequent resistance to chemotherapy.

Drugs including verapamil, quinine, cyclosporin, and calmodulin inhibitors inhibit P-glycoprotein activity, and some of these agents are being evaluated as adjuncts to cytoxic chemotherapy in malignancies associated with the multidrug resistant phenotype. Many normal tissues, including gastrointestinal mucosa, pancreatic and biliary tracts, adrenal glands, renal tubular cells and alveolar cells, express P-glycoprotein. There is therefore, a theoretical potential for increased non-haemopoietic toxicity by inhibition of the efflux of cytotoxic drugs from normal cells. This might be manifested—for example, by increased severity and duration of gastrointestinal mucositis, pulmonary defects, and impaired renal function.



Haematological chart of patient with renal allograft treated for AML showing changes following chemotherapy with DAT 3 + 10, 2 + 7, and Mid AC.

Case report

In March 1988 a 61 year old man received a cadaver renal allograft for end stage polycystic disease. He was treated with cyclosporin 3·5–4·0 mg/kg daily and prednisolone 10 mg daily. The plasma cyclosporin concentration was maintained in the range 75–150 ng/ml.

In September 1989 he developed malaise and fever. The peripheral blood count showed a white cell count of 79 × 10^9/l with 95% blasts. The bone marrow showed 80% AML blasts (M4) with suppression of normal haemopoiesis. Cytogenetic analysis showed a normal 46,XY karyotype. He was treated with daunorubicin 50 mg/m^2, for three doses on alternate days, cytarabine 100 mg/m^2, 12 hourly, and 6-thioguianine 100 mg/m^2, 12 hourly, for 10 days (DAT 3 + 10). He continued to receive cyclosporin 3·5–4·0 mg/kg daily and prednisolone 10 mg daily throughout treatment. His fever was unresponsive to anti-bacterial drugs. He developed moderately severe oropharyngeal candiadiasis which did not respond to topical antifungal treatment. He was given intravenous amphotericin 0·6 mg/kg daily with a good clinical response. Bone marrow examination two weeks after chemotherapy showed complete haematological remission.

Subsequently he received two courses of consolidation chemotherapy: daunorubicin 50 mg/m^2 for two doses on alternate days, cytarabine 100 mg/m^2, 12 hourly and 6-thioguanine 100 mg/m^2, 12 hourly, for seven days (DAT 2 + 7). This was followed after one month by cytarabine 1 g/m^2, 12 hourly, for three days and mitozantrone, 10 mg/m^2 daily, for five days (MidAC). The figure shows the haematological and renal responses to chemotherapy. There were no clinical complications following DAT 2 + 7. After MidAC, however, while severely neutropenic, he developed *Pseudomonas aeruginosa* septicaemia, and despite aggressive antibiotic and supportive treatment he died from acute renal failure and adult respiratory distress syndrome.

Discussion

Myelodysplasia and acute myeloid leukaemia have been described in renal allograft recipients treated with azathioprine.[3–7] We know of only one previous report of the development of acute myeloid leukaemia in such patients receiving cyclosporin.[8] This patient had also received azothiaprine. One further unpublished case is cited in this report. Our patient had been given immunosuppressive treatment with cyclosporin for 18 months before the onset of acute myeloid leukaemia. Although a causal relation between his relatively short duration of immunosuppression and the subsequent development of acute myeloid leukaemia seems unlikely, the possibility cannot be excluded.

Remission induction was achieved relatively easily in our patient. There was no evidence that his concurrent cyclosporin treatment cused increased toxicity to normal tissues or to his grafted kidney. This suggests that inhibition of P-glycoprotein with drugs such as

cyclosporin may not greatly increase the toxicity of aggressive chemotherapy used in the treatment of haematological malignancies. Sonneveld and Nooter reported a patient with resistent AML to whom they administered cyclosporin without any excessive toxicity, although their patient had profound marrow hypoplasia for three weeks.[9]

Septic shock is a well recognised problem in severely neutropenic patients. It is difficult to be sure that our patient's clinical course would have been any different had he not received cyclosporin. Although cyclosporin and other inhibitors of P-glycoprotein may improve the response to chemotherapy, the use of immunosuppressive agents during the treatment of acute myeloid leukaemia does require caution. Non-immunosuppressive cyclosporin analogues may produce the desired positive effects of P-glycoprotein inhibition without increased infection risk.[10]

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Inhibition of urease activity but not growth of Helicobacter pylori by acetohydroxamic acid

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Abstract

The in vitro effects of acetohydroxamic acid (AHA), a potent urease inhibitor, were studied to determine the effect on the urease activity and growth of 38 strains of *Helicobacter pylori*. AHA in concentrations of 50–1000 mg/l had a noticeably reversible inhibitory effect on the urease activity of the organism but no effect on growth.

Helicobacter pylori has a very high urease activity which is thought to be related to its pathogenicity, allowing it to colonise and survive in the harsh gastric environment.[1]

There is a need for a more effective treatment against *H pylori* because currently available treatments are unsatisfactory.[2] Acetohydroxamic acid (AHA) is a potent inhibitor of the enzyme urease.[3–6] AHA has been used in the treatment of urinary tract infections, associated with struvite stone formation, in which urea splitting organisms are important.[7] AHA prevents alkalinisation of the urine by inhibiting urease, thus preventing hydrolysis of urea and subsequent production of ammonia.

The high urease activity of *H pylori* might be inhibited by AHA and we therefore studied this in vitro to determine whether AHA inhibits urease activity and the growth of *H pylori*.

Methods

Thirty three recent clinical isolates and five reference strains (obtained from LCDC, Ottawa) of *H pylori* were grown microaerobically at 35°C for five days. Dense suspensions were made in 3 mmol monobasic sodiumphosphate buffer (NaH_2PO_4) containing a concentration of AHA to approximate a final concentration of 10^8 organisms/ml when