Short reports

Acquired immunodeficiency with disseminated cryptococcosis

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SUMMARY A 9 year old Portuguese boy presented with severe wasting and a disseminated cryptococcal infection that resolved after massive doses of intrathecal and parenteral antifungal agents. Clinical and laboratory findings were consistent with AIDS. Apart from neonatal blood transfusions, there were no identified risk factors for HTLV III infection.

Cerebral cryptococcosis is rare in childhood but is a recognised opportunistic infection in immunodeficient patients.¹ We report the effect of intensive treatment for such an infection in a child with acquired immunodeficiency syndrome (AIDS), who also had an atypical antibody response to human T cell lymphotropic virus (HTLV III).

Case report

The child had a three year history of intermittent abdominal pain, diarrhoea, and weight loss before he presented in Portugal at 9 years of age with epistaxes, microcytic anaemia, and thrombocytopenia. *Giardia lamblia* was found in the stools, and he improved after a course of metronidazole. Two months later he developed fever, convulsions, purpura, and a recurrence of diarrhoea and anaemia. He was given steroids and referred to the United Kingdom.

He had been born at 28 weeks' gestation weighing 1390 g and received two blood transfusions shortly after birth. He recovered uneventfully from measles at 9 months. Mantoux tests in 1979, 1980, and 1983 were negative, despite BCG vaccinations in 1978 and 1980.

Examination showed severe wasting, plaques of oral candida, clubbing of fingers and toes, a 1 cm ulcerating lesion on his nose, and purpura over the lower legs. There was no hepatosplenomegaly or lymphadenopathy. Respiratory and neurological examinations yielded normal results.

Haemoglobin was 109 g/l (mean corpuscular

volume 72 fl), and the platelet count fell to less than $10 \times 10^9/l$ after stopping the steroids. IgG and IgM were shown on his platelets, and the bone marrow had increased numbers of megakaryocytes. His serum contained cold agglutinins of anti-I specificity. No pathogens were found in the stools. *Staphylococcus aureus* was isolated from a discharging left ear. Chest x ray film and barium enema yielded normal results. Liver biopsy, performed under steroid cover to increase the platelet count, showed inflammation of the portal tract with Alcian blue positive capsules typical of *Cryptococcus neoformans*. Large numbers of these organisms were also found in the cerebrospinal fluid (CSF) at lumbar puncture, and a computed tomogram of the brain showed ventricular dilatation and cerebral atrophy. Herpes simplex was isolated from the ulcer on the nose. Serum antibodies to herpes simplex were positive to a titre of 160, although antibodies to cryptococcus were persistently undetectable above a titre of 4.

Immunological and retroviral studies. Serum immunoglobulin concentrations were increased (IgG 19.8, IgA 5.2, and IgM 7.0 g/l). There was persistent inversion of the ratio of helper to suppressor T lymphocytes, and although the total lymphocyte count had increased to $5 \times 10^9/l$ by month 17 there were still only 8% of helper cells (Leu 3a⁺) to 68% of suppressor cells (Leu 2a⁺). The lymphocytes showed markedly decreased reactivity to in vitro stimulation with concanavalin A as measured by production of interleukin-2 and synthesis of DNA.² This diminished DNA synthetic response was partially corrected by adding exogenous interleukin-2, consistent with the presence of an inducible inhibitor of production of interleukin-2 as has been previously described in AIDS.

The patient's serum was negative for HTLV III antibodies by competitive radioimmunoassay³ and remained so over 17 months. His serum, however, was weakly positive at a dilution of one in four on H9 cells infected with HTLV III,³ with no immunofluorescence detected on uninfected H9 cells. In

Figure Changes in peripheral blood and cerebrospinal fluid (CSF) during treatment. Trough CSF drug concentrations after intraventricular amphotericin were 0.8 $\mu\text{g/ml}$ with 0.5 mg given on alternate days and 0.1–0.2 $\mu\text{g/ml}$ with 0.25 μg on alternate days. During the final period of treatment simultaneous serum and CSF concentrations of ketoconazole were 20 and 0.5 $\mu\text{g/ml}$, respectively, and of flucytosine were 40 and 20 $\mu\text{g/ml}$, respectively.

d=Daily; alt d=alternate days; tds=three times a day; qds=four times a day. *Intravenous gammaglobulin (Sandoglobulin) given during an episode of septicaemia with superadded bacterial CSF infection.

addition, using radioimmunoprecipitation⁴ his serum reacted with glycoprotein 120, one of the major envelope glycoproteins of HTLV III, but not with other antigens related to HTLV III. Reverse transcriptase activity was detected after cocultivation of the patient's peripheral blood mononuclear cells with CEM cells,⁵ with which syncytial cell formation was also seen. Sera from both parents were negative for HTLV III antibodies by radioim-

munoassay: more detailed retroviral studies were not performed, but neither parent belonged to any group known to be at increased risk of HTLV III infection.

Response to antifungal treatment. He was treated with oral flucytosine in combination with amphotericin, the latter being given both intravenously and intrathecally through an intraventricular Ommaya

reservoir. The doses used led to apparently adequate levels in the CSF (Figure). Complications included a staphylococcal infection related to the surgical insertion of the Ommaya reservoir and five weeks later a neutropenia, which recovered on temporarily stopping the treatment with flucytosine. Severe potassium depletion from the renal effect of amphotericin required constant monitoring and correction. The reservoir was removed after 18 doses of intrathecal amphotericin because of persistent superinfection, but it was reinstated one month later because cryptococci remained visible in, though could not be grown from, the CSF. A further 17 doses of intrathecal amphotericin were given (with intrathecal hydrocortisone to minimise the risk of chemical ventriculitis). The herpes infection on the nose responded to acyclovir. After five months in hospital he was discharged, having gained 5 kg in weight. Three months later his CSF still contained occasional non-viable cryptococci: further treatment with high dose oral ketoconazole and flucytosine was administered, and the Ommaya reservoir was removed.

At 17 months learning difficulties were noted, as well as persistent asymptomatic thrombocytopenia. The cerebral atrophy was unchanged on a computed tomogram of the brain. Over the next six weeks he developed visual disturbance associated with optic atrophy and spastic paraparesis. Cryptococci were not seen in the CSF, although cryptococcal antigen, initially present to a titre of 5, remained just detectable in neat CSF.

Discussion

The clinical features in this child, including fungal, protozoal, and viral infections, weight loss, and thrombocytopenia, are consistent with AIDS. Furthermore, there is convincing laboratory evidence of retroviral infection, though this was initially unclear because the antibody response to HTLV III was atypical and undetected by our standard radioimmunoassay.³ The neonatal blood

transfusions were a potential source of retroviral infection, raising the possibility that there may be a latency of many years before immunodeficiency becomes overt: unfortunately, the donors could not be traced as the blood bank concerned had since been closed. This case shows that even in an immunocompromised patient large doses of antifungal agents, together with careful attention to the inevitable complications of such treatment, can eventually eradicate cryptococcal infection. Our patient, however, has progressive neurological deterioration: this could be due to a residual effect of the cryptococcosis or its treatment, but cerebral atrophy and myelopathy are now recognised features of HTLV III infection.⁶

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Monitoring spontaneous respiration in the ventilated neonate

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SUMMARY A technique for monitoring the ventilated neonate's own respiratory efforts using a pneumatic capsule apnoea alarm is described.

Most babies, unless very sick or paralysed, continue to breathe while being ventilated, exhibiting their own respiratory pattern and certain respiratory reflexes.¹ The neonate's own respiratory efforts often reduce the efficacy of mechanical ventilation