

## Non-Hodgkin's Lymphoma Following Treatment of Atopic Eczema with Cyclosporin A

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*Sir,*

We report here a patient with severe atopic eczema who was commenced on low-dose cyclosporin A (CyA) for 17 months with good response. Unfortunately, she subsequently developed a high grade peripheral T-cell lymphoma with a fatal outcome.

### CASE REPORT

A 51-year-old woman had a lifelong history of severe atopic eczema. In childhood she had frequent courses of oral prednisolone (between 5 mg and 20 mg per day) and parenteral adrenocorticotrophic hormone (ACTH) (up to 40 units three times weekly). In her twenties and thirties she received

twice-weekly PUVA for 6 months, followed by weekly PUVA for 3 years and monthly PUVA for a further year. Between the ages of 38 and 49 years her eczema was controlled using emollients and a moderately potent topical steroid.

In 1997 she had a severe flare of her disease, which was resistant to intensive inpatient therapy. She was commenced on CyA 3 mg/kg/day (150 mg daily) for 3 weeks. Her eczema responded rapidly and she was maintained on 2 mg/kg/day (100 mg). She remained on this dose for a total of 17 months. There were no renal complications and the drug was well tolerated.

Six weeks after stopping CyA she self-referred with a 4-week history of widespread lymphadenopathy, night sweats and weight loss. Her skin disease remained quiescent. On examination she had generalized lymphadenopathy with large rubbery nodes in her axillae and groin. She had obviously lost weight but there was no hepatosplenomegaly. Her full blood count was normal but her LDH was found to be 2010 (normal range: 230–460 U/l).

Lymph node biopsy showed a high grade peripheral T-cell lymphoma. The tumour was positive for CD3 and CD43 (T-cell markers) and negative for CD20 (B-cell marker). The tumour was positive for CD30 (activated T-cell marker) but negative for anaplastic lymphoma kinase. *In situ* hybridization for Epstein–Barr virus (EBV) was negative.

She was found to have stage IIIb disease and commenced on CLVPP (chlorambucil, vinblastine, procarbazine and prednisolone). Her lymphadenopathy settled following her first course of chemotherapy and she completed five courses of this treatment over 6 months. Unfortunately, she developed a recurrence in the left inguinal nodes after her fifth course and Tru-cut biopsy revealed a high grade transformation. She was given 2 courses of CHOP (cyclophosphamide, adriamycin, vincristine, prednisolone), which led to resolution of the mass, but she developed neutropenic sepsis following each course. She was subsequently treated with radiotherapy to her groin to which she responded well. She was doing well up until 9 months later when she developed a further recurrence in the left submandibular gland, again treated with radiotherapy. She deteriorated following this and was admitted with cachexia, anaemia and a mediastinal mass on her chest X-ray. She died 2 months later, 18 months after cessation of her CyA therapy.

## DISCUSSION

The efficacy of CyA for severe atopic eczema has been well established (1). Doses of CyA used in dermatological conditions are much lower than those used after organ transplantation and the significant adverse effects of hypertension and renal dysfunction are reversible if short-term low-dose CyA is discontinued. CyA is a potent immunosuppressive agent, which is not cytotoxic. It has no appreciable effect on the bone marrow but has a selective inhibitory effect on helper T cells. This effect is said to be largely reversible and the immune function of CyA-treated patients should therefore return to normal after the drug is stopped (2).

Immunosuppressive therapy carries inherent risks involving the occurrence of lymphoproliferative disorders and malignancies. Compared with a normal population matched for age and sex, CyA-treated organ transplanted patients have a 28-fold higher prevalence of lymphomas (3) which is an improvement on the 24–59-fold increased risk in patients receiving conventional immunosuppressive regimens. The majority of

CyA-induced non-Hodgkin's lymphomas are related to EBV, are of B-cell origin, and tend to regress after discontinuing immunosuppression. However, up to 15% of transplant-related lymphomas are of T-cell origin and unrelated to EBV infection (4).

Cytotoxic immunosuppressive therapies may permanently remove certain T-lymphocyte clones that are required for control of latent oncogenic viruses or certain malignant cells that are not replaced in adults following discontinuation (2). Treatment with CyA at a later date causing further suppression of T-cell function may facilitate tumour growth (2). We could postulate then that treatment with oral steroids, ACTH and PUVA may have damaged the T-cell clones in our patient with introduction of CyA at the later date aiding tumour growth. If this is the case then we should be particularly cautious in prescribing CyA for patients who have previously received other potent immunosuppressive drugs.

There are few reports in the literature about lymphoproliferative diseases following the use of low-dose CyA as used in dermatological and rheumatological disease. B-cell lymphoma has been reported in a psoriatic patient treated for 8 months with CyA therapy (5) and cutaneous T-cell lymphoma has been reported in a patient with atopic eczema treated with long-term CyA with regression after discontinuation (6).

To our knowledge this is the first reported case of systemic lymphoma developing in a patient who was treated with low-dose CyA. We accept that the occurrence of lymphoma in this patient may have been coincidental but the risk/benefit ratio for the use of CyA in otherwise fit patients with skin disease should be kept in mind.

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