

Adult T-cell Lymphoma/Leukaemia Developing in a Patient with Psoriasis Treated with Long-term Cyclosporine

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Sir,

Oral cyclosporine is used successfully to treat several dermatological immune-mediated conditions, including atopic dermatitis and psoriasis. An increased incidence of malignant neoplasms has been demonstrated in transplant recipients receiving immunosuppressive therapy with high doses of cyclosporine (1), while the risk of developing lymphomas in patients with psoriasis receiving low doses of cyclosporine therapy appears to be very low (2). We report here a patient with psoriasis who developed lymphoma-type adult T-cell lymphoma/leukaemia (ATLL) after 13 years of a low dose regimen of cyclosporine therapy.

CASE REPORT

A 66-year-old Japanese man had suffered from severe generalized plaque-type psoriasis since 1963. He had previously been treated by Goeckerman treatment; etretinate 75 mg/day for 6 years; psoralen plus ultraviolet A (PUVA) therapy 12 times and methotrexate 7.5 mg weekly for 2.5 months. Cyclosporine was started in 1992 at a dose of 5 mg/kg/day and was reduced to 3 mg/kg/day in 1998 after significant improvement of his psoriasis. His disease was controlled with topical steroids and calcipotriol, and 3 mg/kg/day cyclosporine until February 2005. However, rapidly enlarging, bilateral, cervical and inguinal lymphadenopathies suddenly developed in November 2004. Physical examination also revealed scaly erythemas and psoriatic plaques were distributed on his trunk and all limbs. Laboratory tests revealed a white blood cell count of $8.5 \times 10^9/l$ ($7.6 \times 10^9/l$ neutrophils and $0.4 \times 10^9/l$ lymphocytes), serum lactate dehydrogenase of 390 U/l (115–230 U/l), serum calcium of 8.7 mg/dl (8.6–10.2), C-reactive protein of 5.35 mg/dl (<0.3) and serum interleukin-2 receptor of 34,000 U/ml (135–483). No abnormal lymphoid cells with lobulated or indented nuclei were detected. Other laboratory tests, including data on liver and renal function, showed no abnormal results. Anti-human T-cell lymphotropic virus type-1 (HTLV-1) antibody was positive, which was shown by Western blotting. Serological tests for Epstein-Barr virus (EBV) were consistent with an ancient EBV infection. A computed tomography scan showed the presence of numerous enlarged mediastinal lymph nodes and a stenotic change of the superior vena cava. A bone marrow biopsy was negative for tumour invasion. An inguinal lymph node biopsy specimen disclosed an effacement of the nodal architecture by a polymorphic population of atypical large lymphoid cells (Fig. 1). Mitotic figures were numerous. Immunohistochemical studies demonstrated that most atypical lymphoid cells were positive for CD3 and CD4, but negative for CD8 and CD20. *In situ* hybridization of the atypical lymphoid cells did not show the presence of Epstein-Barr virus (EBV) DNA (EBV-encoded RNA (EBER) probes). Southern blot hybridization analysis of a lymph node demonstrated monoclonal integration of HTLV-1 provirus and clonality of the T-cell receptor (TCR) beta-chain

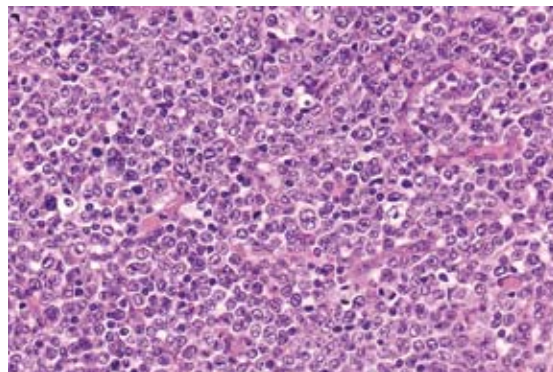


Fig. 1. Pathological findings of an inguinal lymph node. Polymorphic atypical large lymphoid cells with hyperchromatic convoluted or indented nuclei, prominent nucleoli and abundant cytoplasm (haematoxylin and eosin stain, original magnification $\times 100$).

gene rearrangement (Fig. 2). Based on these findings, the patient was diagnosed as having lymphoma-type ATLL.

DISCUSSION

Pharmacological immunosuppression is one of the most important risk factors for malignancies. The most common type of malignant neoplasm among such patients is lymphoma, which has an estimated annual incidence of 1.4–3.6% in recipients of organ transplants who receive cyclosporine (3). The majority of transplant-related lymphomas is of B-cell type and appears to be related to EBV infection (4), however, up to 15% of transplant-related lymphomas are T-cell origin and unrelated to EBV infection (5). On average, lymphoma developed in patients on cyclosporine therapy after 10–12 months of the therapy, while in patients receiving conventional immunosuppressive agents (azathioprine, prednisolone or cyclophosphamide) lymphomas occurred after 3.5–4 years (6). As cyclosporine is used at a lower dose in psoriasis patients and those patients usually do not consume other immunosuppressive agents, the data collected from transplant patients are not directly applicable to patients with psoriasis. A recent study disclosed that the incidence of internal malignancies and lymphomas are not significantly increased in patients with psoriasis receiving low doses of cyclosporine, when compared with the incidence in the general population (7).

Nine cases of lymphomas occurring in psoriasis patients treated with cyclosporine have been reported in

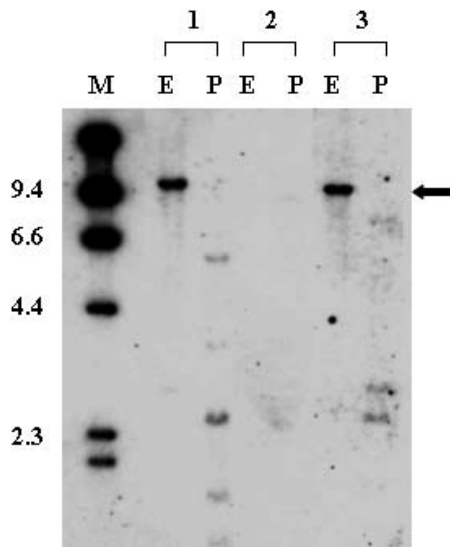


Fig. 2. Southern blot hybridization analysis with *Eco RI* (E) and *Pst I* (P) fragment probe. Note the band of monoclonal integration of HTLV-1 provirus from a lymph node biopsy specimen (Lane 3, E, arrow). Lane 1 is the positive control and Lane 2 is the negative control.

the English literature (8–15). Including our patient, the patients (8 men, 2 women) ranged in age from 35 to 67 years (median 53.7 years). The duration of cyclosporine treatment ranged from 1 month to 15 years (median 4.8 years). Previous therapies included Goeckerman treatment, PUVA, UVB therapy, etretinate, acitretin, methotrexate and infliximab. The types of lymphoma were 4 cases of B-cell lymphoma (8–11), 3 cases of CD30-positive T-cell lymphoma (12–14) and 3 cases of T-cell lymphoma (8, 15). EBV-associated lymphoma was seen in only one case (11). The development of ATLL during cyclosporine therapy is very rare, and there are only 4 anecdotal case reports of ATLL developing in renal transplant recipients. To our knowledge, this is the first case of ATLL in a patient treated with cyclosporine for psoriasis.

In our patient, there was a period of 13 years from the beginning of the cyclosporine therapy to the occurrence of lymphoma-type ATLL. In addition, our patient had been treated with other immunosuppressive therapies, which could have increased his propensity to develop lymphoma. It is difficult to argue that the low dose of cyclosporine was directly related to the development of ATLL in our patient. Thus the causative role of cyclosporine in the development of ATLL is yet to be determined. Nevertheless, it should be stressed that this

putative risk should be taken into consideration when cyclosporine is considered for the treatment of psoriasis.

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