CD30+ Cutaneous Lymphoma in Association With Atopic Eczema

Clair L. Fletcher, MRCP; Guy E. Orchard, MSc; Virginia Hubbard, MRCP; Sean J. Whittaker, MD, FRCP; Richard L. Edelson, MD; Robin Russell-Jones, MA, FRCP, FRCPath

Background: Chronic atopic eczema is not regarded as a precursor of malignancy, and, to our knowledge, there has been only one previous case report of CD30+ cutaneous lymphoma in association with atopic dermatitis.

Observations: We report 4 cases of CD30+ lymphoproliferative disease in young adult patients with active atopic eczema dating from early childhood. Three patients developed primary cutaneous anaplastic large cell lymphoma, of whom 2 developed systemic disease and 1 died. The other patient developed lymphomatoid papulosis type A, which resolved after withdrawal of cyclosporine therapy. No other patient had received immunosuppressive therapy.

Conclusions: Although we have not been able to establish a causative link, we believe that the association of these 2 conditions has not occurred by chance. Biopsies of lesional skin from subjects with atopic eczema exhibit a proportion of CD30 cells, and clonal transformation of this subpopulation might account for the CD30+ lymphomas in our patients.

Arch Dermatol. 2004;140:449-454

Here has been only one previous case report of CD30+ cutaneous lymphoma in association with atopic dermatitis1 to our knowledge. The new World Health Organization classification of tumors of the hematopoietic and lymphoid system includes lymphomatoid papulosis (LyP) and primary cutaneous anaplastic large cell lymphoma (ALCL) as examples of primary cutaneous T-cell lymphoma.2 These entities did not appear in the revised European-American classification,3 but were treated separately in the European Organisation for the Research and Treatment of Cancer classification of primary cutaneous lymphoma.4 Lymphomatoid papulosis is regarded as a condition of uncertain malignant potential, whereas primary cutaneous ALCL is differentiated from nodal ALCL because of its more favorable prognosis, the absence of a t(2;5) chromosomal translocation, and absence of the protein anaplastic large cell lymphoma kinase (ALK).5 Neither condition is Epstein-Barr virus (EBV)–associated, and the cause remains unknown. T-cell clones have been detected in both conditions.

The association of LyP with mycosis fungoides and Hodgkin disease is well described, but it has not been reported previously in conjunction with atopic eczema. Lymphomatoid papulosis can also be associated with CD30+ primary cutaneous ALCL, and the 2 conditions are recognized as representing a spectrum of CD30+ lymphoproliferative diseases.2 Both types of lesion may be seen in the same patient, and patients with LyP type C exhibit borderline lesions, with the histological features of primary cutaneous ALCL but with a tendency to remit spontaneously.

CD30 is a transmembrane cytokine receptor of the tumor necrosis factor receptor family. It is an activation marker expressed by a wide range of neoplasms, including some lymphomas.5 Normal lymphoid tissue also contains a small proportion of large lymphoid cells that express CD30. CD30 lymphocytes may be found in benign inflammatory dermatoses, and the expression of CD30 has been suggested as a marker for a Th2 cytokine response, as exemplified in atopic dermatitis.6

We describe 4 patients with long-standing atopic eczema and primary CD30+ cutaneous tumors. The findings provide some insight into the association between inflammatory dermatoses and a particular subset of primary cutaneous T-cell lymphoma.
CASE 1

A 25-year-old man was referred with a lifelong history of severe, persistent atopic eczema starting in infancy. He had been admitted for inpatient treatment on numerous occasions. He was working as a scientist in toxicology and was otherwise in good general health.

During the ensuing 9 years, he was treated with several systemic treatments, including Chinese herbal medicine, which was ineffective, oral photochemotherapy (receiving 80 treatments, with a cumulative UV-A dose of 861 J/cm²), and concomitant courses of prednisolone and antibiotics. He had also been treated with azathioprine, 150 mg/d, for 5 ½ years, which at times was combined with UV-B phototherapy. Subsequently, he was treated with cyclosporine at a dosage of 2 to 2.5 mg/kg of body weight per day.

Three years later, he presented with a 6-week history of a crusted nodule on his right flank. Further questioning revealed that a few months earlier a similar lesion had been noticed on his trunk that resolved spontaneously, and he subsequently developed further self-healing lesions. Figure 1 illustrates a typical lesion on his right hand. A diagnostic biopsy was performed, which showed a dense nodular infiltrate in the upper and mid dermis composed of lymphocytes, eosinophils, and larger anaplastic cells (Figure 2 and Figure 3). These cells showed abundant cytoplasm and stained positive for CD2, CD3, CD4, and CD30, but not for CD8. These findings were consistent with LyP type A.

Further immunostaining demonstrated that approximately 30% of the cells showed nuclear reactivity for p53 protein. Staining with latent membrane protein 1 was negative, and in situ hybridization for EBV in coded messenger RNA was also negative.

General examination revealed extensive lichenified eczema and bilateral axillary and inguinal lymphadenopathy. A right inguinal lymph node biopsy showed dermatopathic changes. A biopsy from an area of eczema demonstrated focal spongiosis with exocytosis of lymphocytes. The dermis contained a dense perivascular lymphohistiocytic infiltrate with an admixture of eosinophils. A few large CD30 cells were also present scattered within the dermal infiltrate. Analysis of the T-cell receptor (TCR) γ gene using polymerase chain reaction and single-stranded conformational polymorphism showed evidence of an identical T-cell clone in 2 biopsy specimens from cutaneous nodules. Studies on the lymph node biopsy specimen and 2 areas of eczema showed a polyclonal pattern only. The clinical and histological features were consistent with LyP type A in association with severe atopic dermatitis.

Further investigations showed a raised lactate dehydrogenase level at 688 U/L (normal range, 286-580 U/L) and a raised CD4/CD8 ratio of 5 (normal range, 0.7-3.5). A Giemsa-stained blood film showed 4% activated lym-
phocytes (total white blood cell count, 8.1 × 10⁹/L), but no large Sézary cells were seen. T-cell receptor gene analysis of peripheral blood showed no evidence of a T-cell clone, so these activated lymphocytes were attributed to his widespread atopic disease. Analysis for human T-lymphotropic virus 1 was negative. A computed tomographic scan of the chest, abdomen, and pelvis showed bilateral axillary lymphadenopathy, but no other abnormalities.

Initially, his cyclosporine dosage was reduced, but he continued to develop self-healing nodules of LyP. Subsequently, extracorporeal photophoresis was commenced on a monthly basis, and his cyclosporine was discontinued. No further lesions developed, although there was no discernible clinical improvement in his eczema. Five months later, treatment with interferon alfa was started at a dosage of 3 million units 3 times weekly by subcutaneous injection. Several months of therapy failed to produce any clinical benefit, and both treatments were therefore withdrawn.

His atopic eczema is now controlled with methotrexate, 12.5 mg weekly. No further lesions have developed since the withdrawal of cyclosporine.

CASE 2

A 31-year-old man was referred with long-standing atopic eczema from 3 months of age. Over the years, this had required more than 25 hospital admissions. He had received UV-B phototherapy and oral photochemotherapy, as well as several courses of systemic corticosteroids, but had not received any immunosuppressive therapy. He had taken Chinese herbal medicine for 18 months, which had helped his eczema considerably, but had to be discontinued because of the financial burden.

Before his referral, his eczema had been under good control; however, during the preceding 6 months, large grouped nodules had developed around his left elbow, and a solitary nodule had ulcerated on the right side of his nose. By the time he was seen, some of the nodules on his elbow had also ulcerated and were secondarily infected (Figure 4).

A diagnostic biopsy from one of the nodules showed a superficial and deep infiltrate composed of large anaplastic cells that were CD30+ (Figure 5) but ALK-negative. These cells were positive for CD2, CD3, and CD4, but negative for CD8. p53 Nuclear immunoreactivity was also observed in approximately 15% of the atypical cells (Figure 6). These histological features were consistent with a diagnosis of primary cutaneous ALCL.

Palpable lymph nodes were present in the axillae and inguinal areas, but an inguinal lymph node biopsy showed reactive changes only with a small proportion of scattered CD30 cells. Computed tomographic scanning of the abdomen, chest, and pelvis confirmed the peripheral lymphadenopathy, but revealed no other significant abnormality.

Further investigations showed a mildly elevated serum lactate dehydrogenase level at 599 U/L, a lymphopenia of 1.0 × 10⁹/L, negative human T-lymphotropic virus 1 serology, and an absence of circulating Sézary cells. A bone marrow aspirate and trephine biopsy showed no involvement by lymphoma. T-cell receptor gene analysis showed an identical T-cell clone in his skin and peripheral blood. Samples from the lymph node and bone marrow aspirate were polyclonal.

A skin biopsy from an eczematous area showed spongiosis with an upper dermal perivascular lymphohistiocytic inflammatory cell infiltrate, but no lymphocyte atypia and no CD30 cells. T-cell receptor gene analysis showed a polyclonal pattern.

The cutaneous nodules responded to local radiotherapy. His condition remained stable for 1 year before he developed further cutaneous nodules and enlarged lymph nodes in the left axilla and inguinal area. Repeat computed tomographic scanning showed widespread lymphadenopathy, including celiac axis nodes. Repeat lymph node biopsy from the left inguinal area demonstrated complete effacement of the node architecture and replacement by a diffuse infiltrate of large anaplastic CD30 cells, which were ALK-negative. T-cell receptor gene analysis showed a T-cell clone in the lymph node, identical to that detected previously in the skin and blood.
He was referred for an autologous peripheral blood stem cell transplant and underwent harvesting using etoposide and the humanized anti-CD52 monoclonal antibody Campath 1H. Following this, he received debulking chemotherapy with DHAP (dexamethasone, high-dose cytarabine, and cisplatin) and fludarabine phosphate, achieving only a partial remission of his disease.

He subsequently received 1 cycle of CHOP (cyclophosphamide, doxorubicin, vincristine sulfate, and prednisone) chemotherapy. His condition deteriorated, and he died before receiving an autologous transplant.

CASE 3

This 35-year-old woman first had atopic eczema in early childhood. It was well controlled until age 28 years, when she developed extensive lichenified eczema on the limbs. Several courses of oral prednisolone and psoralen–UV-A (PUVA) therapy were only partially effective.

In early 1996, she developed plaques and nodular lesions over her face and upper back. A biopsy showed a dense dermal lymphohistiocytic infiltrate containing large atypical mononuclear cells. Immunophenotypic studies showed that these cells were positive for CD2, CD3, and CD30. There was weak staining for CD4, but CD8 and p53 were negative. T-cell receptor gene analysis at this time revealed a polyclonal pattern. She was mildly anemic (hemoglobin, 10.4 g/dL), but her other laboratory results, including human T-lymphotropic virus 1 serology, were normal or negative. An initial diagnosis of a primary cutaneous CD30+ T-cell lymphoma was made, and she responded to therapy with PUVA. She subsequently developed bilateral axillary lymphadenopathy and multiple infiltrated plaques over her trunk. Computed tomographic scanning showed no other evidence of systemic disease. A further biopsy from a facial nodule showed histological features of a CD30+ ALCL, and on this occasion, a T-cell clone was identified after analysis of the TCR-γ gene. She had a partial response to PUVA plus interferon alfa, but then became pregnant and developed bulky right femoral lymph nodes. Fine-needle aspiration from one of the nodes showed large CD30 anaplastic cells, identical to those in the previous skin biopsies. In view of her pregnancy, she received 80% of the usual dosage of CHOP chemotherapy. She responded favorably, although the enlarged right femoral lymph nodes persisted, requiring treatment with local radiotherapy following the birth of a healthy infant.

Seven months later, she relapsed with widespread lymphadenopathy but no visceral or cutaneous disease. She received a further course of CHOP, followed by an autologous bone marrow transplant. She has remained symptom-free, with no clinical evidence of eczema or lymphoma, for 2 years.

CASE 4

A 28-year-old Hispanic man with lifelong, severe, generalized atopic eczema was referred to the Department of Dermatology at Yale University School of Medicine with multiple cutaneous tumors. He had never received immunosuppressive therapy or PUVA.

A biopsy of a nodule showed atypical CD30 cells, which were positive for CD3 and CD4, but p53-negative. These histological features were consistent with a cutaneous CD30+ ALCL. A biopsy from an area of eczema showed no lymphomatous involvement and no CD30 cells. He had no palpable lymphadenopathy, and staging investigation failed to show any systemic disease. Peripheral blood T-cell subsets were normal, and there were no circulating Sézary cells. Analysis of the TCR genes in peripheral blood and skin biopsies from a nodule and from an area of eczema failed to demonstrate a T-cell clone.

He was treated with superficial radiotherapy to individual tumors and total skin electron beam therapy twice weekly for 8 weeks. Midway through his electron beam course, he commenced extracorporeal photopheresis on a monthly schedule. This combined approach was instigated because of the number of skin tumors that had developed but failed to undergo spontaneous resolution.

Following the commencement of photopheresis, no further cutaneous tumors developed during 9 months. He has remained disease-free for 2 years since cessation of photopheresis, and his atopic dermatitis has cleared almost completely.
This is the first series reporting primary cutaneous CD30+ lymphomas developing in individuals with severe, long-standing atopic dermatitis. Three patients developed CD30+ ALCL, and 1 patient had LyP type A.

All the patients were young, with a mean age of 29 years, and had extensive juvenile-onset eczema persisting into adult life. Primary cutaneous ALCL typically affects older patients with a median age of approximately 60 years. The 5-year survival is 90%. In contrast, 2 of the patients in our series have had an aggressive clinical course, with multisystem disease, and 1 has died.

There are occasional reports of patients with Sézary syndrome and mycosis fungoides who had a preceding history of eczema. However, in the absence of TCR gene analysis, it is difficult to know whether the eczematous lesions represented patch-stage cutaneous T-cell lymphoma (mycosis fungoides). All of our patients had active eczema at the time they developed their CD30+ lymphoma, and it was possible to exclude a diagnosis of erythrodermic cutaneous T-cell lymphoma by biopsy and/or TCR gene analysis.

In all patients except patient 4, TCR gene analysis was carried out using polymerase chain reaction and single-stranded conformational polymorphism analysis as previously described, and in all patients except patient 4 the diagnosis of lymphoma was confirmed by the finding of a T-cell clone in lesional skin. In the 2 patients sampled, a polyclonal pattern was identified in lesional skin from an area of eczema.

CD30 T cells are commonly found in reactive infiltrates, such as insect bites, and may also be seen in patients with atopic skin disease and in dermatopathic nodes. It is therefore conceivable that this subpopulation might undergo clonal transformation, but this would likely be a multistep, multifactorial process. Otherwise, the association between atopic eczema and CD30+ lymphomas would occur frequently. Possible mechanisms leading to the development of a neoplastic cell population include immunosuppression, phototherapy-induced malignancy, and chronic antigenic stimulation of cutaneous lymphocyte-associated antigen-positive T cells, from cutaneous bacteria or superantigens. Lymphomas are well documented in immunosuppressed patients; however, these are generally of B-cell lineage and are commonly EBV associated. None of our patients had EBV, neither by immunostaining (latent membrane protein 1) nor by in situ hybridization for EBV in coded messenger RNA, and all lymphomas showed a T-cell immunophenotype. Only one of our patients had been immunosuppressed, with azathioprine and cyclosporine, and he developed LyP. However, the LyP remitted completely following withdrawal of immunosuppressive therapy.

Phototherapy may be relevant in 3 of the patients. Two patients had received considerable amounts of UV-B and PUVA. p53 Mutations in patients with mycosis fungoides are associated with tumor-stage disease or large-cell transformation. Furthermore, most of these mutations are typical of DNA damage caused by UV-B radiation. It has, therefore, been suggested that UV exposure might promote disease progression or large-cell transformation in patients with patch- or plaque-stage mycosis fungoides. Nonmelanoma skin cancers associated with PUVA also show UV-B-type p53 mutations, suggesting the persistence of p53-mutated cells through an immunosuppressive effect. In our series, the 2 patients showing p53 immunoreactivity had received phototherapy with UV-B and PUVA. Previous investigations have shown that tumor p53 nuclear reactivity correlates closely with the presence of p53 mutations. However, there was insufficient DNA available from either of our patients to confirm this by sequencing, so the possible contribution of phototherapy to the p53-positive cells in these cases must remain speculative.

Another possibility is that tumor cells arise from persistent antigenic stimulation of T cells. Bacterial skin flora, including staphylococci and streptococci, could provide the necessary antigens and superantigens. Cutaneous T-cell lymphoma cells may be stimulated in vitro by staphylococcal superantigens. Staphylococcus aureus and bacterial superantigens are known to exacerbate atopic eczema and other inflammatory skin diseases.

This may be of relevance in our 4 patients, all of whom had severe persistent eczema, with superadded bacterial infection, although this would not easily explain the rarity of CD30+ cutaneous lymphomas in patients with severe atopic dermatitis.

Finally, the reported association between atopic eczema and primary cutaneous CD30+ lymphomas may have arisen by chance. However, this seems unlikely as all 4 patients had atopic skin disease at the time they developed their lymphomas. Furthermore, the age at onset and the aggressive pattern of lymphoma in 2 patients are not characteristic of primary cutaneous CD30+ lymphoma.

Accepted for publication July 24, 2003.

We thank our colleagues who referred patients, and Keely Jenner, PhD, from the Department of Cellular Pathology, Heartlands Hospital Birmingham, England, for undertaking the in situ hybridization studies for EBV in coded messenger RNA.

Corresponding author: Robin Russell-Jones, MA, FRCP, FRCPATH, Skin Tumour Unit, St John’s Institute of Dermatology, St Thomas’ Hospital, Lambeth Palace Road, London SE1 7EH, England.

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