

## Aggressive CD30 Large Cell Lymphoma after Cyclosporine Given for Putative Atopic Dermatitis

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### Key Words

Mycosis fungoides · Cyclosporine · Dermatitis, atopic · Lymphoma, cutaneous

### Abstract

Atopic dermatitis (AD) is not regarded as a predisposing condition for cutaneous T cell lymphoma. Cyclosporine (CsA) is an efficient therapy in AD, and its side effects, including lymphocytic proliferation, are rare at the low dose used in such cases. So far 3 cases of patients who developed cutaneous T cell lymphoma under CsA treatment for atopy have been described. An adult patient with a history of AD received CsA therapy because of an atypical flare-up of his eruption. He rapidly developed papular atypical lesions, then followed by the onset of a voluminous cutaneous tumor leading to the diagnosis of mycosis fungoides (MF) transformed in CD30+ large cell lymphoma with nodal and blood involvement. No improvement occurred after withdrawing of CsA, and he required a polychemotherapy and an allograft. This case illustrates the dramatic evolution of an MF under CsA given in the hypothesis of AD. It stresses the fact that skin biopsies should be taken in case of atypical AD to rule out MF and avoid such an aggressive evolution under immunosuppressive therapy.

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The use of cyclosporine (CsA) therapy for severe atopic eczema is well established [1]. To the best of our knowledge only 2 previous cases of CD30+ cutaneous lymphoma have been reported in patients treated for atopic dermatitis (AD) with CsA [2, 3]. Those 2 cases resolved after interruption of CsA therapy. One case of transient transformation of cutaneous T cell lymphoma (CTCL) has also been reported under CsA [4].

### Case Report

A 37-year-old man had typical AD since the age of 6. The skin lesions showed the typical aspect and distribution of eczema. In early adulthood the eruption was still present and still considered as AD, with several episodes of erythroderma. Nevertheless, improvement was regularly obtained by the use of topical steroids.

In 2002, at the age of 35, cutaneous eruption was no longer controlled by topical treatments. Atypical lesions with an involvement of the trunk and some papules on the chest and back were noticed. The patient was then treated for 1 year with CsA at the dose of 2.5–4 mg/kg daily, without relevant improvement. No cutaneous biopsy was performed at this time, despite the presence of infiltrated lesions and follicular papules.

During the CsA treatment, 1–5 mm erythematous and pruriginous papular le-

sions appeared on the ears and eyebrows (fig. 1). Histopathologic examination of a skin biopsy showed an inflammatory monomorphous lymphocytic infiltrate of the dermis with cystic formations around the follicular ostium. Epidermotropic lymphocytic infiltration was observed, with exocytosis and without spongiosis. The majority of the infiltrating lymphocytes were CD4+. These findings were consistent with a CTCL, but no clonal rearrangement of the T cell receptor was found. Topical treatment with tacrolimus was initiated, and CsA was stopped.

In January 2004, 1 year after the discontinuation of CsA treatment, a voluminous purplish tumor of 10 cm diameter, with subcutaneous infiltration, developed quickly on the right hip (fig. 2), rapidly followed by the onset of similar lesions on the legs. The patient was then referred to us. The initial lesions remained unchanged on the ears and eyebrows, but they extended to the trunk and limbs. There was no lesion typical of eczema. The patient also had general symptoms, i.e. night sweats, a weight loss of 5 kg and marked asthenia. Clinical examination revealed multiple inguinal, axillar and subclavicular enlarged lymph nodes. On blood tests lactate dehydrogenase was at 816 IU/ml (normal = 100–247) and  $\beta_2$  microglobulin at 2.8 mg/ml (normal = <2). Eosinophilia was found at  $5 \times 10^9/l$  (normal = 0.04–0.5). The total lymphocyte count was normal ( $4 \times 10^9/l$ ; normal = 1.5–4), but on subpopulation analysis 36% of them were normal-size lymphocytes CD4+, CD3– and CD8–. The



**Fig. 1.** Papular infiltrated lesion of the eyebrow.



**Fig. 2.** Voluminous tumor of the right hip.

CD4/CD8 ratio was normal, and no Sezary cells were found.

The biopsy of the hip lesion revealed a dense infiltrate of large lymphocytes, mostly widespread with a nodular architecture. No epidermotropism was observed. This infiltrate was dense, monomorphous and composed of large nonanaplastic cells (fig. 3). Immunostainings on tumoral cells revealed CD30+, CD3-, CD4-, CD8-, CD20- and ALK- (anaplastic lymphoma kinase); >70% of the infiltrating cells were large CD30+ lymphocytes. The histopathological findings of the papular lesions of the legs revealed a lymphocytic infiltrate in the upper dermis composed of atypical small lymphocytes with cerebriform nuclei. Large atypical cells were sparse in this infiltrate. Those cells were CD3+ and CD4+, with a small CD30+ cell contingent.

The same monoclonal rearrangement of the T cell receptor  $\gamma$ -chain was identified in the CD4+ and CD30+ subpopulations in the tumor, papular lesions and blood, attesting to the transformation of mycosis fungoides (MF) in an aggressive CD30+ CTCL. Bone marrow aspiration and lumbar puncture were normal. The lymph nodes were widely invaded by CD30+ large cells. The diagnosis of transformed MF in this atopic patient treated with CsA a few months before was established, according to the new WHO-EORTC classification of cutaneous lymphoma [5]. He received cyclophosphamide, doxorubicin, vincristine and

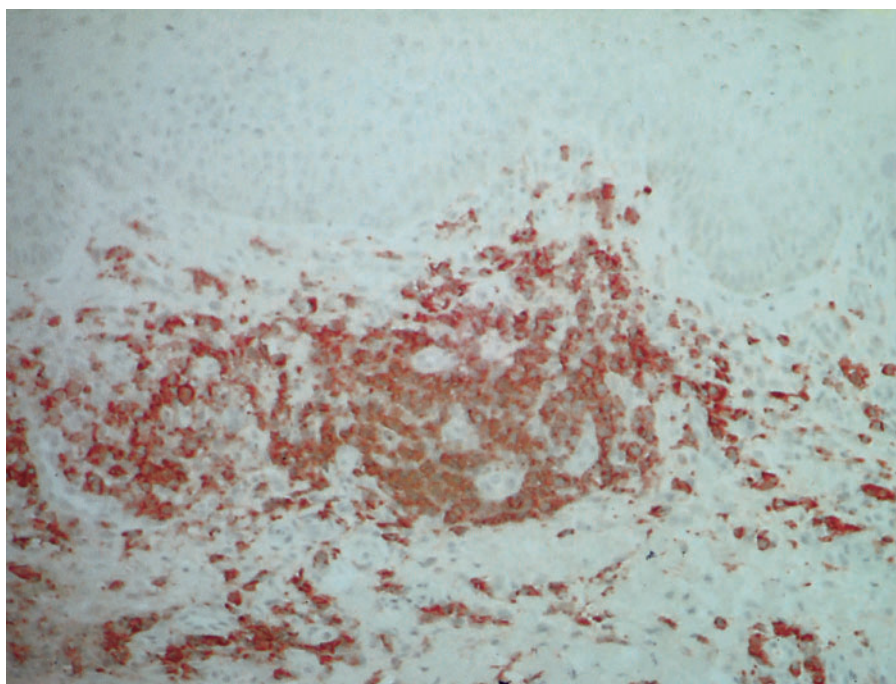


**Fig. 3.** CD30+ immunostaining of hip lesion: dense infiltrate of large CD30+ lymphocytes. This infiltrate was dense, monomorphous and composed of large nonanaplastic cells.  $\times 400$ .

prednisone (CHOP)-like multiagent chemotherapy with temporary improvement. He relapsed after a few months; an autograft did not permit a clinical remission. He finally received an allogeneic hematopoietic stem cell transplantation after con-

ditioning regimen including total body irradiation, fludarabine and busulfan. He is now in complete remission of the lymphoma, with severe cutaneous manifestations of graft-versus-host disease.

## Discussion

To the best of our knowledge, this is the first case report of an aggressive CD30+ transformed CTCL developing in an atopic patient treated with CsA. The initial history, clinical aspect and evolution were consistent with the diagnosis of AD. Nevertheless, the clinical presentation became atypical 4–5 years before the diagnosis of cutaneous lymphoma and was interpreted as a steroid-resistant evolution of eczema. We hypothesized that the eruption already corresponded to an early-stage MF. CsA therapy did not alleviate the disease but induced a flare-up of the cutaneous lesions, with onset within a few months of a transformation of MF.

CsA was initially evaluated in the treatment of CTCL and has clearly not shown sustained benefit [6, 7]. Three cases of patients with AD developing cutaneous CD30+ lymphoma have already been reported [2]. They developed primary cutaneous anaplastic large cell lymphoma. None of them had received immunosuppressive oral treatment. Two of them had a rapidly aggressive clinical course with nodal involvement, and 1 of them died [2].

Two cases of Sezary syndrome concerning a young man with severe AD have been published [8, 9]. However, in a retrospective study including 157 cases of CTCL, Mehrany et al. [10] concluded that the association between atopic eczema and CTCL was not significant.

Nevertheless, what is uncommon in the case reports [2, 4], and in our case, is the young age at the onset of the lymphoma and the rapidly aggressive course of the disease.

CsA used in transplant recipients is associated with an elevated risk of cancer and especially lymphomas [11, 12]. When used at low doses in dermatological indications (up to 5 mg/kg daily), the risk seems to be lower: only 2 reports of systemic lymphomas [13, 14] and 3 of cutaneous lymphomas are found in such conditions. During CsA treatment of psoriasis, 2 CTCL [15, 16] and 1 CD30+ anaplastic large cell lymphoma [17] have been described, and they all regressed after cessation of the treatment. In 1 recent case CsA was associated with infliximab before the onset of CTCL [18].

During the treatment of severe AD with CsA, 2 cases of cutaneous T cell proliferation have been reported. CsA was ini-

tiated in a 25- [2] and a 39-year-old [3] patient. They developed a type A lymphomatoid papulosis and a CD30+ large cell lymphoma, respectively, and both cases improved after interruption of CsA. A third case concerns a flare-up of an atopic eczema considered as psoriasis and then treated with CsA, leading to a large cell transformation in lymph nodes after 1 month. This disease regressed completely after cessation of the drug. A biopsy of skin lesions finally revealed MF [4].

We think that in our patient the diagnosis of CTCL was unfortunately not made initially, and CsA therapy had a role not only in the flare-up of CTCL but also facilitated the aggressive transformation in a CD30+ large cell lymphoma.

In our view histopathological examination of skin biopsies is required before initiation of CsA therapy eruption in patients supposed to have an atypical AD. If the biopsy is not absolutely typical of eczema, with any doubt for CTCL, CsA should not be administered.

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