

Sézary syndrome in a young man with severe atopic dermatitis

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Summary

Sézary syndrome (SS) is a rare cutaneous T-cell lymphoma. SS usually develops *de novo*. We describe a 23-year-old man with a proven history of severe atopic dermatitis since childhood, who developed SS. This case contributes to the discussion about the possibility of a relationship between inflammatory dermatitis, atopy and subsequent SS. We provide criteria that should be fulfilled to define such an association.

Key words: atopic dermatitis, cutaneous T-cell lymphoma, Sézary syndrome.

Sézary syndrome (SS) is an uncommon form of cutaneous T-cell lymphoma (CTCL), defined historically by the triad of a chronic exfoliative pruritic erythroderma, lymphadenopathy and the presence of atypical lymphoid cells named Sézary cells (SCs) in the peripheral blood and in the skin.¹ The term pre-Sézary erythroderma syndrome (PSES) was introduced to describe a non-diagnostic dermatitis preceding the overt clinical picture of SS, defined by the combination of chronic erythroderma and less than 10% SCs in the peripheral blood. Patients with PSES may have a history of atopic dermatitis (AD) and/or an atopic background.²

There is an ongoing debate about whether there exists a direct relationship between benign dermatoses, atopy and subsequent CTCL.^{3,4} Reports of the onset of mycosis fungoides (MF)/SS-type CTCL at younger ages in patients with preceding AD support the possibility of an association. However, more often the MF lesions in young patients do not develop from pre-existing AD, neither are they associated with an atopic constitution.^{5,6} We present a patient with SS who at a very young age had as a conspicuous feature SS preceded by severe AD. The clinical, histological, immunohistochemical and genotypic data are discussed in the context of the sequential occurrence of severe AD and CTCL. This case report may give insight into the pathobiology of the development of SS. We propose criteria which, when they are fulfilled, make an association between AD or an atopic constitution and subsequent CTCL likely.

Case report

In 1985, a 20-year-old male house painter was seen with severe AD, present since birth. At the age of 14 years, the symptoms had worsened over a period of 12 months and, over the next 4 years, he became erythrodermic, with severe itching and lymphadenopathy. In 1985, his total serum IgE was 9800 kU/L (normal <150), with IgE specific for grass pollen and house dust mites being detected. Laboratory investigations, including an eosinophil count, were normal. The patient was treated with moderately potent topical steroids, in combination with oral prednisone, 7.5 mg/day, and hydroxyzine.

In 1988, his skin condition worsened with larger areas of lichenification, excoriation and prurigo nodularis (Fig. 1). Large firm lymph nodes were present in the axillae and groins. Blood leucocytosis was present (white cell count $13 \times 10^9/L$) with 40% lymphocytes with large, indented nuclei. Punch biopsy specimens of the skin revealed an acanthotic epidermis with hyperkeratosis and spongiosis. The papillary dermis was infiltrated by small lymphocytes but in the epidermis the lymphocytes were slightly larger than usual and had hyperchromatic, indented nuclei. Small blast cells were seen in the epidermis as well as in dermal perivascular cell infiltrates. Immunohistochemistry revealed an infiltrate composed of T cells, which showed a normal immunoprofile of T-cell markers (CD2 +, CD3 +, CD4 +, CD5 +). Morphometry showed that about 5% of the lymphocytes had a nuclear contour index (NCI) of up to 12 (normal up to 6.5).

Biopsy of an axillary lymph node showed infiltration

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Figure 1. Severe atopic dermatitis with prurigo nodularis is evident on the legs.

of small lymphocytes with hyperchromatic, indented nuclei. The histopathological diagnosis was early involvement of SS. Peripheral blood smears revealed that more than 90% of the lymphocytes had unusual irregular nuclei with a cell diameter ranging from 7 to 9 μm , NCI ranging from 11 to 16 and occasional blast cells. The CD4/CD8 ratio was 25.

Rearrangement studies of the peripheral blood with a DNA probe directed against the C β gene of the T-cell receptor showed evidence of the presence of a monoclonal T-cell population. Enzyme immunoassay techniques did not reveal antibodies specific for human T-cell lymphotropic virus type I in the serum.

The diagnosis of SS was established and treatment was started with chlorambucil, 4 mg/day, and prednisone, 20 mg/day (1988–90). The skin lesions improved for a period of about 2 years and itching disappeared. In 1992, the skin disease deteriorated with increasing pruritis. Radioallergosorbent tests revealed a total IgE

of 19,929 kU/L. Laboratory investigations were otherwise normal. Punch biopsy specimens of the skin then revealed an epidermotropic infiltrate consisting of large SCs. Bone marrow examination revealed sporadic SCs. The SC count in the peripheral blood ranged from 6% to 23% (white cell count $4 \times 10^9/\text{L}$). Rearrangement studies revealed no monoclonality at this time. A computed tomographic scan of the abdomen did not reveal enlarged lymph nodes.

Chlorambucil, 6 mg/day, and prednisone, 20 mg/day, were recommenced. After 1 years, the therapy was changed to an alternating scheme of etoposide, 50 mg/day for 2 weeks per month, combined with interferon alpha-2b, 3×10^6 IU subcutaneously, three times weekly. The skin disease did not respond to this therapy. During this period the SC counts in the peripheral blood varied from 6% to 25%. In November 1994, the patient had an exacerbation of the erythroderma. A punch biopsy specimen of the skin revealed large SCs with lichenoid changes in the epidermis (Fig. 2). The SCs were CD2+, CD3+, CD4+, CD5+. Pentostatin and prednisone, 20 mg/day, were started in combination with psoralen-ultraviolet A therapy.

In March 1995, the patient developed acute necrosis of the retina due to a herpetic infection. He was initially treated with intravenous aciclovir, 10 mg/kg every 8 h, and afterwards with oral aciclovir, 400 mg twice daily. The severity of his skin lesions did not change. His general condition worsened due to lung infection with *Pneumocystis carinii* and he died at the age of 30 years from respiratory insufficiency in November 1996. No autopsy was performed.

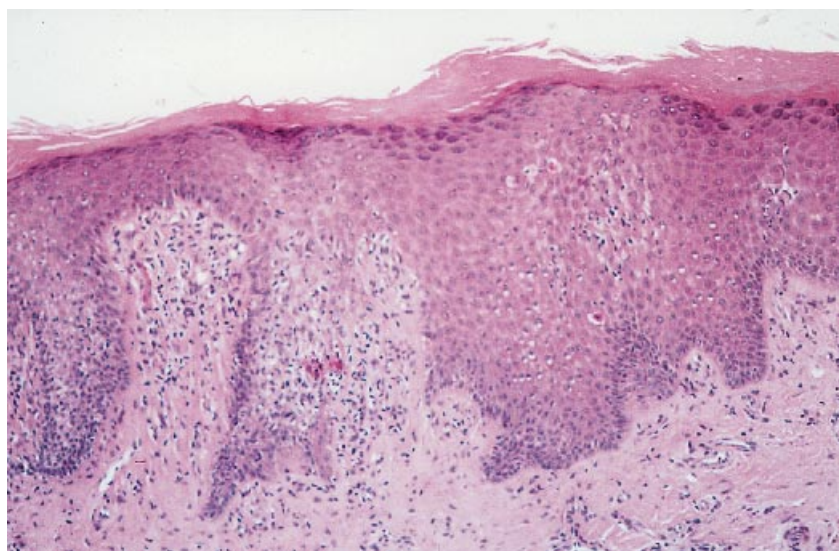


Figure 2. Photomicrograph showing acanthosis, hyperkeratosis, spongiosis and infiltration of the epidermis with numerous large lymphocytes (haematoxylin and eosin; original magnification, $\times 100$).

Discussion

In this patient, a diagnosis of AD was made on clinical criteria including sensitivity to inhalation allergens. The eczema was severe, but remission could be induced. The transition into SS was gradual, and was characterized by an exacerbation of the erythroderma with lymphadenopathy and high percentages of circulating SCs which also appeared in skin biopsies in association with features of eczema. The patient fulfilled the criteria for the diagnosis of SS according to the European Organization for Research and Treatment of Cancer (EORTC) classification criteria.¹ It appeared that the pre-existing severe AD and atopy were related to the subsequent development of SS. It has been reported that non-diagnostic erythrodermic dermatitis may precede the overt clinical picture of SS.¹ In some patients, the diagnosis of PSES can be made,² but this phase was not seen in the patient presented here. A study from our department on 28 patients with an idiopathic erythroderma indicated that only two (7%), including the patient presented here, showed progression of their erythroderma into CTCL.⁷

AD and other types of eczema rarely progress to erythroderma.³ When erythroderma develops from AD, exacerbation of pre-existing AD lesions usually precedes generalization. Clinical symptoms more similar to SS, such as intense pruritis, alopecia, palmar and plantar hyperkeratosis and onychodystrophy, may be present.⁸ The histopathology of erythrodermic AD gives the characteristic features of eczema. Loss of pan-T-cell antigens does not occur in AD but is an important observation of diagnostic relevance in CTCL.⁹ In general AD, chronic dermatitis and atopy are not significantly associated with CTCL.⁴ AD followed by SS has been reported only once before, in a 44-year-old woman.³ In a study of patients with PSES, five of 18 patients had either a personal or family history of atopy.² Studies on the mechanism of the relation between atopy and AD indicate that atopy may not directly induce AD, but instead may severely aggravate AD through non-specific enhancement of inflammation, such as by generating FcεRI + antigen-presenting cells, which strongly stimulate T cells reactive to environmental proteins and even self antigens.¹⁰

We hypothesize that patients with pre-existing severe chronic AD or an atopic constitution are predisposed to develop SS when they have 'SCs in the making' (genotraumatic cells),¹¹ and that they develop SS at much younger ages. In analogy to AD, the tumour cells in SS may belong to a 'bystander cell population', and exhibit

features of their former place in the immunological network; these SCs are continually influenced by growth factors. In this context, it is also tempting to speculate on the role of atopy with elevation of total serum IgE levels, which has been described in several cases of MF, SS and PSES.¹² The patient described here had allergen-specific serum IgE, and therefore the rise in IgE could be explained by an atopic predisposition. In general, high IgE levels in non-atopic patients with SS, in the absence of allergen-specific IgE, can also be explained by a mechanism of aspecific induction of a latent atopic constitution³ or increased IgE production by B cells mediated by cytokine secretion by CD4 + T cells.¹²

As well as an atopic constitution, depressed T-cell values and T-cell function may also favour a malignant clone. This situation can be found both in association with AD⁸ and in patients with SS.¹³ The occurrence of an acute herpes zoster necrosis of the retina and *P. carinii* pneumonia in our patient could be explained by the atopy but may also be due to immunosuppression caused by the therapy. Finally, bacterial toxins, acting as superantigens, have been implicated as a contributory mechanism in CTCL.⁴ Superantigens also play a part in exacerbation of the disease in patients with AD.⁸ Therefore, chronic antigenic stimulation might have contributed to the transformation.

Research into the relationship between AD and subsequent CTCL, as suggested in earlier case reports and in the present report, can be facilitated by long-term follow-up and *in vitro* studies in which SCs are stimulated under conditions occurring in atopy. In the case of AD it is known that antigen-specific T cells can be cultured from lesional skin.¹⁴ However, in the case of SS, stimulation of *in vitro* proliferation of SCs by specific antigens may be hampered by culture conditions, the absence of the specific antigen, or lack of proliferation of SCs *in vitro*. If these studies are not possible, we suggest that the following criteria should be fulfilled to relate a pre-existing AD and subsequent CTCL: first, the pre-existing benign dermatosis has definitely been diagnosed as AD by specific clinical criteria, in combination with sensitivity to allergens, or as non-specific benign dermatitis by histology and the absence of a monoclonal lymphoid population. Secondly, this benign dermatosis characteristically shows an exceptionally severe course. However, it should respond at least partially to the appropriate treatment. Thirdly, a strong argument for a relationship may be an unusually young age at diagnosis of the subsequent CTCL. Fourthly, a definite diagnosis of SS is made according to the criteria

proposed by the EORTC lymphoma study group in the subsequent disease course.¹ Fifthly, the transitional phase is characterized by a gradual clinical transition between the benign and the malignant skin disorder, and lastly, atypical lymphoid cells appear within the context of the already present benign infiltration.

References

- 1 Willemze R, Kerl H, Sterry W *et al*. EORTC classification for primary cutaneous lymphomas: a proposal from the cutaneous lymphoma study group of the European Organization for Research and Treatment of Cancer. *Blood* 1997; **90**: 354–71.
- 2 Winkelmann RK, Buechner SA, Diaz-Perez JL. Pre-Sézary syndrome. *J Am Acad Dermatol* 1984; **10**: 992–9.
- 3 Rajka G, Winkelmann RK. Atopic dermatitis and Sézary syndrome. *Arch Dermatol* 1984; **120**: 83–4.
- 4 Lambert WC. Inflammatory precursors of mycosis fungoides. In: *Basic Mechanisms of Physiologic and Aberrant Lymphoproliferation in the Skin* (Lambert WC, Gianotti B, van Vloten WA, eds), Vol. 265. New York: Plenum Press, 1991: 217–30.
- 5 Zackheim HS, McCalmont TH, Deanovic FW, Odom RB. Mycosis fungoides with onset before 20 years of age. Review of 24 patients and report of a case diagnosed at age 22 months. *J Am Acad Dermatol* 1997; **36**: 557–62.
- 6 Burns MK, Ellis CN, Cooper KD. Mycosis fungoides type cutaneous T-cell lymphoma arising before 30 years of age. Immunophenotypic, immunogenotypic and clinico pathologic analysis of nine cases. *J Am Acad Dermatol* 1992; **27**: 974–8.
- 7 Sigurdsson V, Toonstra J, van Vloten WA. Idiopathic erythroderma: a follow up study of 28 patients. *Dermatology* 1997; **194**: 98–103.
- 8 Hanifin JM. Atopic dermatitis. *J Am Acad Dermatol* 1982; **6**: 1–13.
- 9 Wick MR, Ritter JH, Humphrey PA, Swanson PE. Immunopathology of non-neoplastic skin disease. A brief review. *Am J Clin Pathol* 1996; **105**: 417–29.
- 10 Röcken M, Schallreuter KU, Renz H, Szentivanyi A. What exactly is 'atopy'? *Exp Dermatol* 1998; **77**: 97–104.
- 11 Kältoft K, Bisballe S, Sterry W *et al*. Sézary syndrome is characterized by genotraumatic cells. In: *Basic Mechanisms of Physiologic and Aberrant Lymphoproliferation in the Skin* (Lambert WC, Gianotti B, van Vloten WA, eds), Vol. 265. New York: Plenum Press, 1991: 401–15.
- 12 Preesman AH, van de Winkel JGJ, Magnusson CGM *et al*. Cell bound IgE and increased expression of Fcε-receptors on dendritic cells in cutaneous infiltrates of mycosis fungoides. *Clin Exp Immunol* 1991; **86**: 246–51.
- 13 Heald P, Yan SL, Edelson R. Profound deficiency in normal circulating T-cells in erythrodermic cutaneous T-cell lymphoma. *Arch Dermatol* 1994; **130**: 198–201.
- 14 van der Heyden FL, Wierenga EA, Bos JD, Kapsenberg ML. High frequency of IL-4 producing CD4+ allergen-specific T lymphocytes in atopic dermatitis lesional skin. *J Invest Dermatol* 1991; **97**: 389–94.