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CLINICAL REPORT

Sudden Onset of an Aggressive Cutaneous Lymphoma in a Young Patient with Psoriasis: Role of Immunosuppressants

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Psoriasis is thought to be associated with an increased risk of lymphoma. We report here the first case of an aggressive primary cutaneous pleomorphic T-cell lymphoma in a patient with psoriasis. The 36-year-old patient, who had previously been treated successively with methotrexate, ciclosporin and etanercept, presented with rapidly growing nodules on the leg. A biopsy confirmed a stage IVa primary cutaneous pleomorphic T-cell lymphoma. Despite treatment with pegylated liposomal doxorubicin, the disease progressed and the patient died 5 months later. This case of pleomorphic T-cell lymphoma was remarkable in both its extremely rapid onset and the aggressive nature of the disease. The onset of this disease in a patient with psoriasis who had been previously treated with immunosuppressive drugs and a tumour necrosis factor (TNF)-α blocker is of major interest. Only eight cases of cutaneous lymphomas associated with treatment with TNF-α blockers have been published previously. Most of these eight cases related to anti-TNFα antibodies; only two were linked to etanercept. *Key words: psoriasis; cutaneous lymphoma; TNF-α blocker; immunosuppressant.*

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Psoriasis is a common chronic inflammatory disease of the skin and joints, which affects approximately 1–2% of the population. It has been shown that patients with psoriasis are at higher risk of developing a malignancy and this risk is greater for patients with severe disease (i.e. patients with psoriasis treated with systemic agents) (1). Nevertheless, studies of the association between psoriasis and lymphoma have shown conflicting results and the frequency and aetiology of this association remain unclear (2). It may be due to the pathogenesis of psoriasis or to the multiple immunosuppressants used in the treatment of psoriasis. Regarding the pathogenesis of psoriasis, experimental evidence suggests a primarily T-lymphocyte-based immunopathogenesis. Excessive Th1 and Th17 lymphocyte activity in psoriatic skin has been demonstrated. Chronic antigenic stimulation in psoriasis may lead, after a variable period of time, to a dominant clone in the skin and then evolution towards a cutaneous T-cell lymphoma (CTCL) (3). Alternatively, lymphomas may be induced by the systemic immunosuppressive therapies used to treat psoriasis, such as ciclosporin, methotrexate and tumour necrosis factor (TNF)-α blockers, which are often used consecutively in the same patient (4). We report here the first case of a primary cutaneous pleomorphic T-cell lymphoma with acute evolution in a young patient with psoriasis previously treated with methotrexate, ciclosporin and etanercept.

CASE REPORT

A 36-year-old man with a 10-year history of psoriasis, which had been classified as severe for one year, had previously been treated with acitretin (Soriatane®, Roche, France) for 6 months (35 mg/day) and methotrexate (Novatrex®, Wyeth pharmaceuticals, France) for 3 months (20 then 25 mg/week) with no improvement. The patient had no other relevant medical history and was not taking any other medicine. The psoriasis was severe (Fig. 1) with a Psoriasis Area and Severity Index (PASI) score of 25 and a Dermatology Life Quality Index (DLQI) of 17. Its diagnosis was confirmed histologically by the presence of hyperkeratosis, parakeratosis and acanthosis, and by the absence of a monoclonal T-cell population in a T-cell receptor gamma gene rearrangement analysis performed using PCR. Treatment with etanercept (Enbrel®, Wyeth pharmaceuticals, France) (50 mg twice a week) was initiated in March 2007. Three months of treatment yielded no improvement. Etanercept was then discontinued and ciclosporin (Neoral®, Novartis pharma SAS, France) (3 mg/kg/day) was introduced in July 2007. Two months later, the patient's cutaneous lesions worsened and he developed cellulitis in his right leg. Ciclosporin was discontinued, and in November 2007 acitretin (25 mg/day) was re-introduced in combination with narrow-band ultraviolet (UV)-B. Two months later, multiple dense red-to-violaceous nodules of firm consistency appeared on the patient's lower left leg over the course of a few days (Fig. 2), accompanied by two large, firm inguinal lymphadenopathies.

Histopathaological analysis of a nodule biopsy specimen revealed a dense atypical pleomorphic lymphoid

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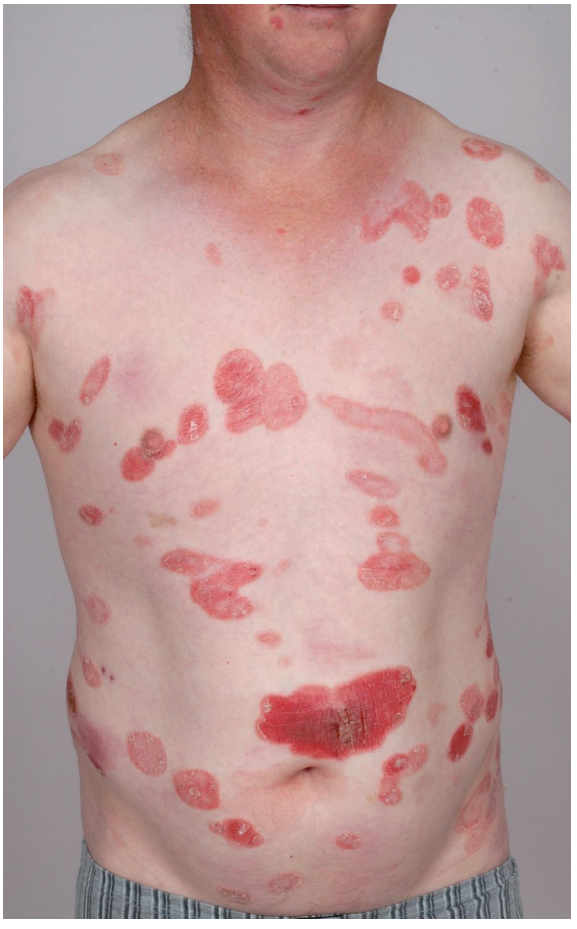

Fig. 1. Severe cutaneous psoriasis with characteristic erythematous squamous plaques, involving 50% of the body surface area.

infiltrate in the dermis, and slight epidermotropism (Fig. 3a). The atypical cells expressed CD3 and CD4, but not CD8 or CD30 (Fig. 3b). Analysis of T-cell receptor gamma gene rearrangements by PCR revealed a monoclonal T-cell population. The results of *in situ* hybridization tests performed on tumour tissue to detect Epstein-Barr virus (EBV) (using EBER probes), cytomegalovirus (CMV) and herpes simplex virus (HSV) were negative. Analysis of a inguinal lymph node biopsy showed infiltration of atypical medium-to-large lymphoid cells with irregular nuclear contours. A computed tomographic (CT) scan of the chest, abdomen and pelvis and a bone marrow biopsy provided no evidence of an extracutaneous lymphoma. Further investigations revealed lymphopaenia with an absolute lymphocyte count of 0.9×10^9/l (normal range 1.5–4.0×10^9/l) and a raised CD4/CD8 ratio of 4.6 (normal range 0.7–3.5). The patient tested negative for human immunodeficiency virus (HIV), CMV and hepatitis A, B and C in serological tests. The EBV serology revealed a previous infection without reactivation. The diagnosis of a stage IVa primary cutaneous CD4+ pleomorphic T-cell lymphoma (T3 N3 M0) was made.

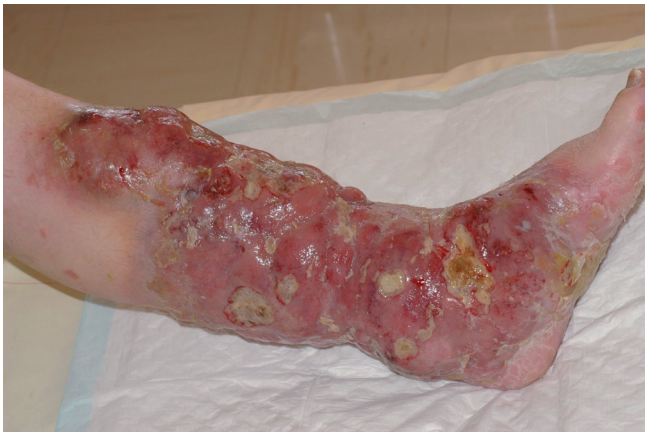

Fig. 2. Multiple dense red-to-violaceous nodules of firm consistency appeared on the lower left leg over the course of a few days.

Treatment with pegylated liposomal doxorubicin Caelyx® at a dose of 40 mg/m^2, administered intravenously once every 4 weeks, was initiated in February 2008. Although the patient partially responded to the first two infusions, his disease then progressed rapidly and he died in July 2008.

DISCUSSION

This case of primary cutaneous CD4+ pleomorphic T-cell lymphoma was remarkable in both its extremely rapid onset and aggressive evolution. Furthermore the patient's young age (36 years) was unusual, as cutaneous pleomorphic T-cell lymphomas usually affect adults who are in their fifties or sixties. The aggressive profile of this cutaneous lymphoma raises questions about the importance of his history of psoriasis and of the role of the consecutive use of 3 immunosuppressive treatments: methotrexate, etanercept and ciclosporin.

Psoriasis and lymphomas

The question of the association between psoriasis and an increased risk of lymphoma has already been raised, since other Th1-mediated diseases, such as rheumatoid arthritis (5) and systemic lupus erythematosus (6), are known to be associated with an increased risk of lymphoma. Fifteen primary studies regarding the risk of lymphoma in patients with psoriasis have been published to date and their results are conflicting (2, 7). Six studies investigated the relationship between a history of selected medical conditions and the risk of lymphoma within population-based case-control studies of lymphoma (7–12). Only two of them showed an increased risk of lymphoma associated with a history of psoriasis (10, 12). Another study, using the same methodology but focussed only on the risk of mycosis fungoides (MF), was conducted in 2003 (13). Among the different medical conditions studied, the highest odds ratios (OR) for MF were found in patients who

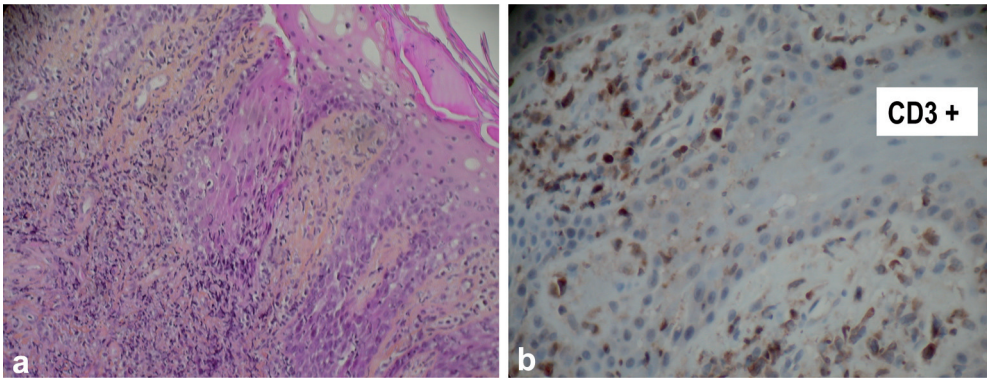

Fig. 3. (a) Punch biopsy demonstrates a dense atypical pleomorphic lymphoid infiltrate in the dermis (haematoxylin-eosin, original magnification ×100). (b) The phenotype of the atypical cells was CD3+, CD4+, CD8–, CD30–.

had reported a history of psoriasis. In addition, eight population-based cohort studies have evaluated the risk of lymphoma in patients with psoriasis. Among them, two related to patients with psoriasis previously treated with psoralen plus ultraviolet A (PUVA) therapy (14, 15). Neither detected a significant increase in the risk of lymphoma. Three studies related to patients hospitalized for psoriasis (16–18). One of them showed a significantly high standardized incidence ratio (SIR) for non-Hodgkin's lymphoma (NHL) (17) and the other two a significantly high SIR for MF (16, 18)). Finally, three large studies were performed using databases (1, 2, 19). Margolis et al. (1) found an increased risk of lymphoma, both for patients with psoriasis who received systemic therapies and for those who did not. In the largest study to date (2, 19), using a general practice research database in the UK, Gelfand et al. (2) showed that the adjusted relative risk of lymphoma was significantly increased, both in mild and severe psoriasis, and that the strongest association of lymphoma with psoriasis was for CTCL.

The conflicting results in these studies probably stem from differences in study sample size and design, type of lymphoma and the severity of psoriasis. Finally, analysis of the literature enables us to conclude that the association between psoriasis and lymphoma is not consistent supported. The magnitude of this association appears to be modest and the strongest association of lymphoma with psoriasis occurs for CTCL (2, 13, 16, 18).

Obviously, the misclassification of an early epidermotropic CTCL as psoriasis could have resulted in false positive associations (20), but this risk seems very low and therefore could not completely explain this increase in the risk of CTCL in patients with psoriasis. In our case, it can be dismissed because: 1) the psoriasis was confirmed histologically (twice); 2) T-cell clones were absent in a cutaneous biopsy (repeated three times); and 3) the lymphoma was pleomorphic and not an epidermotropic CTCL.

Another hypothesis is that the increased risk of CTCL in psoriasis patients may be linked to the pathogenesis of psoriasis. The pathophysiology of psoriasis involves excessive Th1 and Th17 lymphocyte activity, increased activity of antigen-presenting cells, and the production of inflammatory cytokines such as TNF-α and interferon (INF)-γ. This chronic antigenic stimulation in psoriasis could possibly lead to a dominant clone emerging and subsequent evolution towards CTCL. In our patient, the *in situ* role of a Herpes-type virus can be eliminated by the negative result in *in situ* hybridization.

Immunosuppressants and lymphomas

There is a known relationship between the use of immunosuppressive therapies, particularly ciclosporin, and the development of lymphoproliferative malignancies. The vast majority of these immunosuppression-related lymphoproliferative disorders occur in the context of organ transplantation (21, 22).

In relation to our case, the link between the three immunosuppressive drugs prescribed consecutively to the patient and the onset of a cutaneous lymphoma is obviously questionable, since the cumulative duration of drug-induced immunosuppression was limited (8 months) and the time interval between the introduction of the first immunosuppressive drug and the onset of the lymphoma was short (10 months).

The carcinogenic risk of ciclosporin has been suspected for many years. However, ignoring the transplantation issue, the use of ciclosporin in dermatology for the treatment of psoriasis, atopic dermatitis or other inflammatory diseases does not seem to be associated with increased malignancy (23–25). Moreover, the risk of developing lymphomas in patients treated with low doses of ciclosporin over a short period of time is considered to be low (23, 25). Only two cases of primary cutaneous lymphoma have been reported in patients with psoriasis (26) and atopic dermatitis (27), respectively.

Regarding methotrexate, the 2001 World Health Organization (WHO) classification of tumours of tissues recognizes a category of lymphoproliferative disorders (LPD) associated with its use (MTX-LPD) (28). The vast majority of cases develop in patients with rheumatoid arthritis, but it occasionally occurs in patients with dermatomyositis and psoriasis (29). These MTX-LPD

rarely involve the skin (30, 31). In immunocompetent patients, the induction of primary cutaneous lymphomas by methotrexate is rare, with only one single report of folliculotropic mycosis fungoides in a psoriasis patient who was treated with methotrexate (32). In addition, methotrexate is used for the treatment of CTCL.

Etanercept, a soluble human TNF-α receptor, attenuates inflammatory and immune response induced by TNF-α. Currently used to treat inflammatory disorders, such as rheumatoid arthritis, ankylosing spondylarthritis and psoriasis, it may also reduce host defence against malignant neoplasms (33) and, like other TNF-α blockers, is suspected to increase the risk of developing a malignancy. Nevertheless, an increased risk of lymphoma in patients treated with etanercept has not been demonstrated in observational cohort studies, and etanercept is now considered to be the TNF-α blocker causing the fewest lymphomas (34, 35).

Only eight cases of primary cutaneous lymphoma linked to treatment with TNF-α blockers have been reported to date (36–42). The patients concerned were treated for rheumatoid arthritis, ankylosing spondylitis and psoriasis. These cases related mainly to anti-TNF-α antibodies (infliximab and adalimumab). Only two of them related to etanercept. The first involved a 69-year-old patient treated for psoriasis with etanercept for 18 months who developed Sézary syndrome (37). The second concerned a subcutaneous panniculitis-like T-cell lymphoma that occurred in a 50-year-old patient treated for aggressive rheumatoid arthritis with etanercept for 6 years (41). There has also been one case of etanercept exacerbating undiagnosed mycosis fungoides (43). These few cases linking cutaneous lymphomas with treatment with TNF-α blockers may have involved pre-existing CTCLs that were kept in check by cellular immunity. The suppression of immune responses by TNF blocker treatment may then have allowed the lymphoma cells to grow unopposed. Our case is the first of a primary cutaneous CD4+ pleomorphic T-cell lymphoma arising after treatment with TNF-α blockers.

This case highlights the complicated link between psoriasis, lymphomas and immunosuppressants. Since the use of TNF-α blockers is becoming more common in the treatment of psoriasis, continued vigilance is warranted. Large prospective post-marketing cohort studies to assess the safety of these TNF-α blockers in patients with psoriasis are needed to clarify the exact impact of these new treatments on the risk of lymphoma, especially in patients with severe psoriasis previously treated with phototherapy, ciclosporin and methotrexate.

The authors declare no conflicts of interest.

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