

## Cutaneous Pseudolymphoma Following Administration of Lornoxicam

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Sir,

Since aspirin was introduced over a century ago, many new anti-inflammatory agents have been marketed. NSAIDs are currently the most commonly prescribed agents in Western medicine (1). Their widespread use has resulted in a number of well-documented adverse reactions. These most frequently involve the gastrointestinal tract, causing discomfort, nausea and diarrhoea or, occasionally, bleeding and ulceration (2). Cutaneous reactions mainly include urticaria, angioedema, fixed drug eruption, pruritus, photosensitivity and, in severe cases, Stevens-Johnson syndrome and toxic epidermal necrolysis (3).

Lornoxicam (chlortenoxicam) is a new selective cyclooxygenase-2 (COX-2) inhibitor of the oxicam class, with analgesic, anti-inflammatory and antipyretic properties (4). Lornoxicam has a tolerability profile characteristic of an NSAID. No pseudolymphomatous reaction has been reported before.

### CASE REPORT

A 44-year-old Greek man presented with a generalized eruption that had appeared 5 days before his referral to our hospital. Two weeks prior to his admission the patient had suffered from severe back pain, for which he was prescribed oral lornoxicam 8 mg (Xefo®) twice daily. Ten days after initiation of the treatment the eruption appeared. The patient did not report being on any other medication. His personal and family history was otherwise unremarkable.

Clinical examination revealed several asymptomatic, well-defined, erythematous plaques covered by yellow scales located on the trunk and limbs (Fig. 1). Furthermore, hyperkeratosis of the palms and soles with areas of erosions and crusting was



Fig. 1. Psoriasiform erythematous-squamous plaques of the chest and abdomen.

observed, as well as erythema and scaling of the paronychia region of the fingers. The axillary nodes were palpable.

The following laboratory tests were negative or within normal limits: complete blood cell count, erythrocyte sedimentation rate, C-reactive protein, protein electrophoresis, immunological quantitative tests for immunoglobulins, tests for complement components (C3, C4), rheumatoid factor, antinuclear antibodies (ANA), and computerized tomography scan of the thorax and abdomen.

A skin biopsy from a trunk lesion was performed. Histological examination showed hyperkeratosis with parakeratosis and considerable acanthosis and spongiosis in the epidermis (Fig. 2). Epidermotropism of lymphocytes with formation of Darier-Pautrier-like intra-epidermal micro-abscess was noted. Some of these lymphocytes were characterized by atypical features, i.e. lobular or incised nuclei (Fig. 3). The same features were also seen in the epithelium of a few hair follicles. The papillary dermis appeared oedematous with dilated blood vessels and a moderate to severe perivascular infiltrate, consisting mainly of small lymphocytes, with a few histiocytes and eosinophils. Immunohistochemistry showed most of the lymphocytes (including the intra-epidermal atypical ones) to be CD3- and CD5-positive, i.e. of a T-cell immunophenotype. Immunostaining also showed a CD4:CD8 ratio close to 1. A few CD20-positive B-lymphocytes and CD68 (clone PGM1)-positive histiocytes were also noted. No CD30-immunopositive cell was seen. The aforementioned histological features were those of a cutaneous atypical lymphoid infiltration. Two eventualities were discussed: either patch stage mycosis fungoides (MF) or a drug-induced cutaneous pseudolymphoma; the second being more probable due to the results of CD4 and CD8 immunostaining.

PCR study of the skin biopsy did not reveal a monoclonal rearrangement of the T-cell receptor gamma gene.

Microscopic examination of a peripheral blood smear did not show any pathological findings. A bone marrow biopsy showed only a mild erythroblastic reaction.

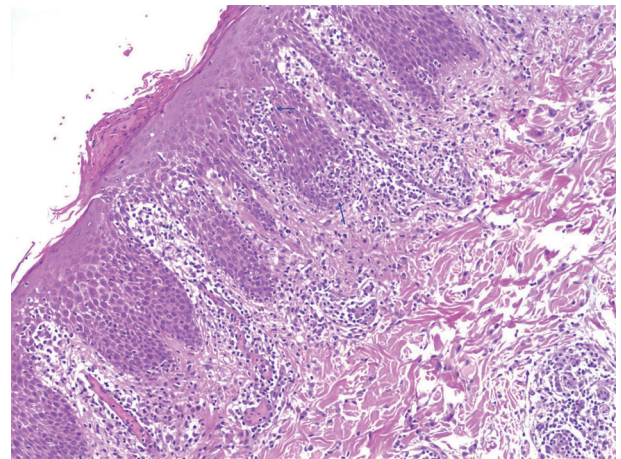


Fig. 2. Hyperkeratosis with parakeratosis, acanthosis, spongiosis and exocytosis with Pautrier-like micro-abscesses in the epidermis. There is moderate mixed inflammatory infiltration in the dermis (H&E  $\times 10$ ).

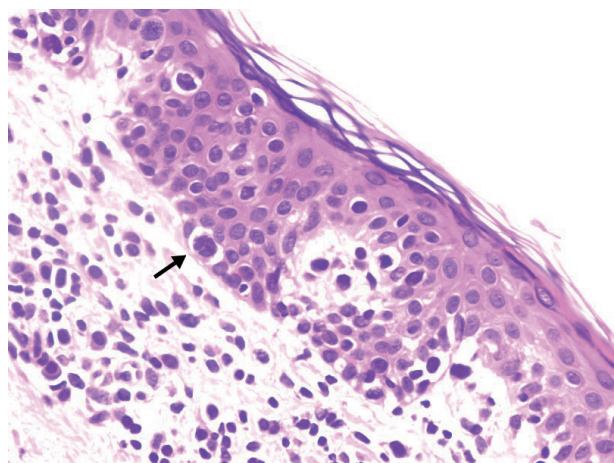


Fig. 3. A lymphocyte with atypical cerebriform nucleus in the epidermis (H&E  $\times 40$ ).

The patient began treatment with oral methylprednisolone 16 mg twice daily. At the same time, lornoxicam was discontinued. Within 4 weeks the rash had improved significantly and the patient was discharged with instructions to taper his steroid dosage and return for regular follow-up. After 6 months, complete remission of the rash had been achieved with no signs of recurrence.

At the 12-month follow-up visit, we conducted skin prick tests (SPTs) and intradermal tests (IDs) with standard preparations of Xefo<sup>®</sup> using 1:1000, 1:100 and 1:10 dilutions in 0.9% saline (4 mg/ml). All tests were performed on the volar aspect of the forearms. Histamine phosphate 2.7 mg/dl (Stallergenes, Paris, France) and normal saline served as positive and negative controls, respectively. Tests readings took place after 20 min for immediate reactions and after 24 h and 72 h for late reactions. In SPTs a wheal diameter  $>3$  mm and in IDs an increase in the initial wheal of  $\geq 3$  mm in diameter associated with a surrounding flare, were considered positive reactions. In addition, patch testing with 1/10 dilution and the commercial regimen of Xefo<sup>®</sup> was performed on the upper back. Finn chambers were removed after 48 h for initial interpretation and further readings were performed at 72 h and 96 h. No positive reactions were recorded in any of the above tests. Provocation tests with lornoxicam were not approved by the ethics committee of our hospital.

## DISCUSSION

Cutaneous pseudolymphomas have been classified according to the predominant cell type (B-cell, T-cell or mixed) and by the distribution of the infiltrate (5). The clinical spectrum is broad and includes maculopapular eruptions, vesiculopustular or purpuric lesions, patch-stage MF-like lesions, or more severe aspects, such as erythroderma or tumoural eruption (6). Histologically, one or more of the following patterns can be assumed: MF-like, a CD30+ lymphomatoid reaction, lymphocytoma cutis, or follicular mucinosis (7). Epidermotropism of atypical lymphocytes and formation of Pautrier micro-abscesses are characteristic features. Genotypic analysis may occasionally demonstrate a rearrangement of the T-cell receptor-gamma gene (8). Progression to overt cutaneous lymphoma has been observed in a minority of cases. Clonal populations may be observed in

benign conditions and is not an exclusive hallmark of cutaneous lymphoma. Nevertheless, patients with B- or T-cell clones and persistent lesions, should be observed closely for emergence of a lymphoma (6).

Cutaneous pseudolymphomas may represent exaggerated reactions to diverse external stimuli, including drugs (6, 9). The drug may not be the provocative agent per se, but may promote an aberrant immune response to an antigen that may be the drug itself or some other stimulus. These types of reactive patterns occur most commonly in the setting of systemic immune dysregulation or multidrug therapy, especially when drugs known to alter lymphocyte function are used (7). Nevertheless, the underlying mechanisms are largely unknown. A case in which a lymphomatoid drug reaction occurred after the intake of two structurally unrelated drugs that interfere with angiotensin II function, suggests that angiotensin II may play a role in the pathogenesis (10).

Drugs most frequently incriminated for the development of cutaneous pseudolymphomas include phenytoin and, less commonly, other anticonvulsants, angiotensin converting enzyme (ACE)-inhibitors and antihistamines. Rare cases have been reported with bromocriptine and cefuroxime (7, 11).

Drug-induced hypersensitivity syndrome (DHS) and drug-induced cutaneous pseudolymphoma are nowadays distinguished (12). DHS is considered as a reaction induced by a complex interplay among several herpesviruses (Epstein-Barr virus, HHV-6, HHV-7 and cytomegalovirus), antiviral immune responses and drug-specific immune responses. It is likely to be mediated by antiviral T-cells that cross-react with the drug (13). DHS is characterized by acute widespread eruption, fever, enlarged lymph nodes and multi-visceral involvement. Atypical lymphocytes are also present in the skin infiltrate. DHS is associated with a mortality rate of 10%, whereas drug-induced cutaneous pseudolymphomas always have an excellent prognosis, although it may take a long time for the eruption to clear even after the cessation of causative agents (8).

Depending on the type of reaction, treatment of cutaneous pseudolymphomas may involve systemic or intralesional corticosteroids, antibiotics, surgical excision for solitary lesions, radiotherapy and immunosuppressants (6).

In our patient, the onset of the eruptions followed the administration of lornoxicam. Clinical presentation, histology, immunophenotyping and molecular studies were suggestive of cutaneous lymphoid infiltrate rather than a true cutaneous lymphoma. The benign course of the eruption, its gradual remission after discontinuation of lornoxicam and the administration of systemic steroids, are all in support of the benign nature of the reaction.

To our knowledge, this is the first case causally relating anti-inflammatory agents and benign or reactive cutaneous lymphoid infiltrates.

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