Naproxen-induced pseudolymphoma syndrome: a case report

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ABSTRACT
Drug-induced pseudolymphoma syndrome is a rare form of adverse cutaneous drug reaction. Its clinical and histological presentation may mimic mycosis fungoides, which sometimes leads to misdiagnosis and unnecessary treatments. We describe the case of a 65-year-old man with a generalized pruritic and confluent maculopapular eruption. His history of skin lesions was concordant with medication and resolved after discontinuation. However, microscopic examination showed characteristic features of mycosis fungoides, including Pautrier-like microabscesses and cerebriform nuclei of atypical lymphocytes. The immunohistochemical study showed CD4/CD8 infiltrate ratio to be 1 in the epidermis. The histopathological result of a second skin biopsy was compatible with drug eruption. This experience demonstrates that combining clinical history, histological and immunohistochemical findings is crucial for a definite diagnosis of PLS.

Introduction
Pseudolymphoma syndrome (PLS) was first reported by Chaiken et al in 1950. PLS is a rare form of adverse cutaneous drug reaction with clinicopathological features similar to that of mycosis fungoides. In the literature, antiepileptic agents are the most frequently cited offending medications for PLS. In this report, we presented a case of naproxen-induced PLS that histologically mimics mycosis fungoides.

Case report
A 65-year-old man, a sufferer of benign prostate hyperplasia and diabetes mellitus type 2, received regular medical attention (tamsulosin HCl, tolterodine for benign prostate hyperplasia, acarbose, glimepiride for diabetes mellitus more than 1 year) in a tertiary medical center in Central Taiwan. Due to an episode of fever, nausea, vomiting and persistent epigastralgia, he was admitted to the hospital. Empiric antibiotics with intravenous cefazolin and gentamicin, medication for benign prostate hyperplasia and diabetes mellitus, as well as acetaminophen and metoclopramide were prescribed. During hospitalization, abdominal computed tomography with contrast enhancement showed pancreatic cancer and surgical excision was recommended. But the patient was discharged against medical advice. After discharge, naproxen, levofloxacin and drugs for benign prostate hyperplasia and diabetes mellitus were prescribed. Three days after discharge, he had a fever (up to 39°C) and itchy skin rashes covering the whole body except the palms and soles (Figure 1). Physical examination revealed confluent maculopapular eruptions with pruritus on the trunk and all four limbs, but no enlarged lymph nodes. Laboratory investigations revealed leukocytosis (13.9×10⁹/L), eosinophilia (1.0×10⁹/L), and atypical lymphocytes (0.3×10⁹/L). Liver function tests showed a mildly elevated aspartate aminotransferase level (1.0 μkat/L), and increased alkaline phosphatase (3.9 μkat/L). Naproxen was discontinued and prednisolone (10 mg bid) was prescribed.
Results from skin biopsy of the forearm showed Pautrier-like microabscesses in the epidermis. Using a high power field, mononuclear infiltrates with cerebriform nuclei were easily identified in the lymphocytic infiltrates. Focal vacuolar change of basal keratinocytes without necrotic keratinocytes was also observed (Figure 2). The above features were suggestive of mycosis fungoides. Immunohistochemical analysis of the infiltrate revealed most of the medium-sized atypical lymphocytes were CD3 positive, and a mixture of CD4 and CD8 cells was observed in the epidermis (Figure 3).

The cutaneous lesions resolved with residual erythema after 1 week of oral prednisolone (Figure 4). A second skin biopsy was then performed to exclude mycosis fungoides. Histological findings showed a few necrotic cells in the basal layer and an infiltrate in the upper dermis. This infiltrate was composed of lymphohistiocytes and some eosinophils. No epidermotropism or atypical lymphoid cells were found in the upper dermis (Figure 5). Thus a definite diagnosis of drug eruption was made, and naproxen was identified as the offending drug. The steroid was discontinued after 2 weeks.
Figure 3  Immunohistochemical staining showing (A) CD3 positive lymphocytes, (B) CD20 negative lymphocytes, (C) CD4 positive lymphocytes, (D) CD8 positive lymphocytes in the epidermis and dermis (CD3, CD20, CD4 and CD8 respectively, all at 100x).

Figure 4  Cutaneous rash (A) on the trunk and (B,C) four limbs almost resolved except for residual erythema on the thigh.

Figure 5  Skin biopsy of the left thigh. (A) Parakeratosis and mild infiltration in superficial dermis (H&E, 40x). (B) Few dyskerototic cells in the basal layer of epidermis (H&E, 200x). (C) Lymphohistiocytes and some eosinphils in upper dermis (H&E, 400x).
of treatment. No recurrence of symptoms occurred in the 3-month follow-up period.

Discussion

Drug eruptions mimicking mycosis fungoides clinically or histologically are rare. Such disorders were first described after the introduction of hydantoin and its derivatives for the treatment of convulsive disorders in the early 1940s. Historically, the term drug-induced pseudolymphoma is used to describe two kinds of adverse drug eruptions. The first is an adverse drug eruption histologically mimicking a cutaneous lymphoma, which was then referred to as PLS. The second is a hypersensitivity syndrome which presents fever, cutaneous eruption, lymphadenopathy, eosinophilia, and hepatosplenomegaly, known as drug rash with eosinophilia and systemic symptoms. Bocquet et al differentiated PLS from drug rash with eosinophilia and systemic symptoms based on clinical presentation, and suggested limiting PLS to cases with slow onset plaques or tumors. However, because these two entities may not only exhibit similar histological findings but also overlapping clinical features, the nosological characteristics of these drug eruptions remain unresolved.

The pathogenesis of PLS is not understood, and it maybe a multifactorial process. The offending drugs perturb lymphoid function in vitro and may promote blast transformation and impair T-cell suppressor function to induce an exaggerated lymphocyte response to exogenous antigenic triggers. This may be exhibited as a drug-induced dysregulated immune reaction to the drug itself, to some other drugs, or to a non-pharmacological antigen. This theory is supported by in vivo evidence of disturbance of the immune system by the offending drugs.

Clinically, the 3 major symptoms of PLS are fever (up to 38–39°C), lymphadenopathy and skin rash. The manifestations of lymphadenopathy may or may not be present and histological examination of the lymph nodes may reveal either a benign lymphoid hyperplasia or a pseudolymphoma pattern. Skin rash may include a morbilliform maculopapular eruption with pruritus in the extremities, including the palm and sole, face and trunk, and less commonly, periorificial papules or generalized pustular lesion. Other associated symptoms include facial edema, hepatosplenomegaly, vomiting, headache, arthralgia, pharyngitis and conjunctivitis. The majority of patients suffer only mild hepatic injury and recover within a few weeks of the cessation of the causative agent. However, when hepatitis is severe, the prognosis is often poor. One study reported a mortality rate of 10–50%. Furthermore, hematological abnormalities are common in PLS, including leukocytosis, eosinophilia, and atypical lymphocytes, at times with lymphocytosis, monocytosis, aplastic anemia, hyper- and hypo-gammaglobulinemia, coagulation disorder and nephritis. PLS usually develops within 3 months of using the causative drug, although it may also develop 1 week to 2 years after exposure to the drug, or sooner at rechallenge. Implicated drugs include phenytoin, carbamazepine, sodium valproate, gemcitabine, gold, the clonidine patch and Gleevec.

Histologically, a band-like infiltrate with cerebriform nuclei in the dermis and possible Pautrier-like microabscesses in the epidermis often make PLS indistinguishable from mycosis fungoides. In 2003, Choi et al proposed a number of histological features that might be used to identify PLS, including more obvious spongiosis and papillary edema, more necrotic keratinocytes, mitosis, mixed inflammatory cell infiltrates and denser cellular infiltration in the dermis than in the epidermis. Immunohistochemically, the 1 to 1 CD4/CD8 infiltrate ratio was consistent with the reactive process, and therefore allowed for diagnosis of PLS. While the clinicopathological and molecular features might make it difficult to differentiate PLS from mycosis fungoides, resolution after drug withdrawal is the diagnostic gold standard.

In the case we presented, mycosis fungoides is strongly histologically favored due to the presence of Pautrier-like microabscesses and cerebriform nuclei of lymphoid cells without necrotic keratinocytes or papillary edema in the biopsy specimen. However, after drug withdrawal, the skin lesions resolved, which facilitated a diagnosis of PLS. The second skin biopsy results further confirmed the diagnosis. Magro and Crowson proposed that non-steroidal anti-inflammatory drugs may perturb lymphocyte function and induce cutaneous pseudolymphoma. Based on the clinical history, the diagnosis of naproxen-induced PLS was established.

The most important therapeutic step is the discontinuation of the offending drug. Although systemic steroids are widely used in the acute phase of disease, it is unclear whether steroids can significantly alter the disease process. Symptomatic therapies for fever with antipyretics should be prescribed carefully to avoid aggravating liver toxicity. Topical steroids and antihistamines could be prescribed for cutaneous rash and pruritus.

In conclusion, we reported a case of naproxen-induced PLS, histologically mimicking mycosis fungoides. The diagnosis was established based on the clearing of the skin lesions upon discontinuation of the offending drug. A second skin biopsy confirmed the benign nature of the lesions. This experience demonstrates that combining clinical history, histological and immunological findings is crucial for a definite diagnosis of PLS.

References