

Bullous Wells' Syndrome Associated with Non-Hodgkin's Lymphocytic Lymphoma

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Sir,

Described by Wells (1) for the first time in 1971 as relapsing granulomatous dermatitis associated with eosinophilia, and subsequently renamed eosinophilic cellulitis (2), Wells' syndrome is a rare form of dermatitis whose broad morphological spectrum ranges from more typical cellulitis-like manifestations to less common bullous vesicular lesions (3, 4).

We describe here a case of a female patient with Wells' syndrome localized to the lower limbs associated with non-Hodgkin's lymphocytic lymphoma/B-cell chronic lymphoid leukemia (B-cell CLL).

CASE REPORT

A 73-year-old woman came to our attention because of the onset of red/violet erythematous lesions of the lower limbs with a purpuric appearance accompanied by pyrotic and pruritic symptoms. One lesion on the medial surface of the right leg presented a taut bulla of about 1 cm diameter with serous content, whereas an erosion due to a previous bulla and multiple smaller bullous lesions with serous or sero-haematic content involved the lateral surface of the left leg (Fig. 1).

The patient reported that she had experienced two similar episodes in the previous 20 days, which had been interpreted as dermatitis due to exogenous causes and, after being treated with oral antibiotic and anti-histamine therapy combined with topical cortisones, had resolved within about one week.

The patient's general condition was good. The only aspect of note in her medical history was the removal of a sigma adenocarcinoma (staged T3;G2;N0) 2 years previously, for which she was undergoing regular follow-up. A general physical

examination revealed palpable bilateral inguinal and axillary lymph node swelling.

Laboratory tests revealed leukocytosis (white blood cell count (WBC) $12.1 \times 10^3/\mu\text{l}$) with eosinophilia ($1.74 \times 10^3/\mu\text{l}$; eosinophils 14.3% neutrophils 48%, lymphocytes 31.2%, monocytes 6.5%, basophils 0.2%), total immunoglobulin E (IgE) = 751 IU/ml, C-reactive protein (CRP) 1.25 mg/dl, erythrocyte sedimentation rate (ESR) in the first hour 60 mm; viral markers (Epstein Barr virus, cytomegalovirus, hepatitis A, B and C virus), cryoglobulin, ANCA, LAC, ANA, ENA and anti-DNA antibodies were all negative.

Histopathological examination of the lesion on the left leg showed an epidermis characterized by multiple, sometimes confluent vesicles containing serum and eosinophil granulocytes. The underlying papillary dermis was markedly oedematous, with focal and minimal erythrocytic extravasations and an interstitial eosinophil granulocytic infiltrate. The reticular dermis was infiltrated by a large number of prevalently perivascular lymphocytic elements and numerous perivascular and interstitial eosinophil granulocytes, which also extended along the interlobular hypodermal septa and, to a lesser extent, the hypodermic lobules. The reticular dermis also showed some small and isolated flame figures (Fig. 2).

The diagnosis of Wells' syndrome was made on the basis of the clinical picture and the histological findings, together with a negative direct immunofluorescence test (5).

Having excluded pharmacological, infective, vasculitic and inflammatory causes, the subsequent instrumental and laboratory investigations were aimed at identifying a possible relapse of the patient's previous neoplastic disease. Complete abdominal ultrasonography, chest radiography and colonoscopy were negative, as was a search for tumour markers. The physical examination findings of numerous swollen inguinal and axillary lymph nodes therefore drew our attention to a possible underlying lymphoproliferative disease, and a subsequent lymph node biopsy revealed a picture compatible with a diffuse, small-cell non-Hodgkin's B lymphoma/B-cell CLL, which was confirmed by a bone marrow biopsy.



Fig. 1. A taut bulla with serous content on the medial surface of the right leg. Sequela of a previous bulla and smaller lesions on the lateral surface of the left leg. Red colour around lesions is due to application of eosin 2% in water.

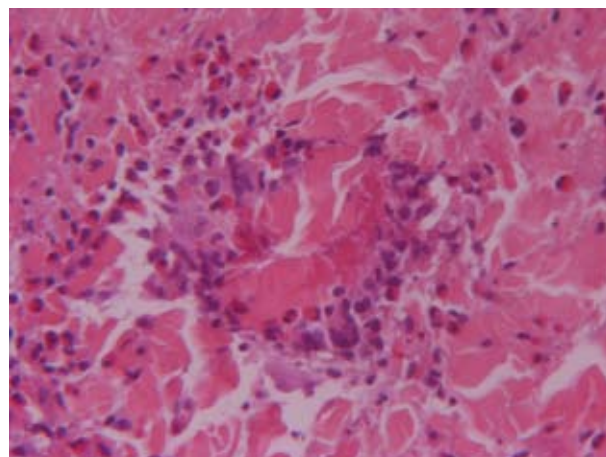


Fig. 2. Histological image of the lesion clearly showing the presence of a central collagen nucleus surrounded by numerous eosinophils and histiocytes forming a typical "flame figure" (haematoxylin-eosin; enlargement $\times 400$).

Systemic steroid (methylprednisolone 20 mg/day), anti-histamine therapy (hydroxyzine 25 mg twice daily) combined with topical antibiotic treatment (fusidic acid cream twice daily) led to the clinical resolution of the lesions within 15 days, after which the steroid was tapered over 3 weeks to discontinuation and only anti-histamine therapy was maintained (hydroxyzine 12.5 mg twice daily).

Given the patient's age and haematological picture, the haematologists currently looking after the patient have decided that no therapy is necessary, only close monitoring.

DISCUSSION

Wells' syndrome is a rare form of inflammatory dermatitis of unknown pathogenesis that is characterized by its clinical polymorphism (1, 3).

It is typically distinguished by the appearance of patches of red-violet erythematous lesions or cellulitis-like plaques, usually accompanied by a slight burning sensation and pruritus (1); after a few weeks, the red-violet erythema is replaced by grey-blue lesions. However, more rarely, it may take the form of papulous, nodular, papulonodular (5) or bullous lesions (4). In 50% of cases the skin manifestations are associated with peripheral eosinophilia whose progress follows that of the disease, returning to normal levels in the case of clinical remission (3).

Its histological appearance is characterized by a diffuse dermal infiltrate of eosinophils and histiocytes that surround nuclei of amorphous or granular material, associated with fibres of dermal connective tissue known as "flame figures" (1), which are typical of, but not specific to, Wells' syndrome (5).

The dermatosis may resolve spontaneously or have a chronic-relapsing course, with an irregular response to therapy.

Various triggering factors have been identified, including drugs, infections (type 2 Herpes simplex virus) (6), parasites (4), insect bites or stings (5), lymphoproliferative diseases (13), vasculitis (Churg-Strauss syndrome) (7), chronic inflammatory diseases (ulcerative colitis) (8) and neoplasias. The literature includes a number of well-documented cases associated with subcutaneous injections of etanercept (9) and adalimumab (10), and with squamous cell carcinomas (11) and colon adenocarcinomas (12).

In our case, the manifestations of Wells' syndrome allowed us to reveal an underlying non-Hodgkin's lymphoma. In our opinion, a search for lymphoproliferative processes should be considered a fundamental step in the diagnostic work-up, particularly in the presence of vesico-bullous lesions, because there are published reports of a possible association between bullous Wells' syndromes similar to insect bites or stings and lymphoproliferative diseases (13).

Systemic drug therapeutic options include anti-histamines, corticosteroids (14) and cyclosporin (15), and there are reports of cases successfully treated with griseofulvin, minocycline and dapsone (14). Topical corticosteroid

(15) and antibiotic therapies (15) are also efficacious, although the therapeutic response is slower.

In the case described here, the bullous clinical manifestations and associated pruritus led us to prefer a therapeutic approach based on oral systemic corticosteroids and anti-histamines, combined with topical antibiotics. This led to an optimal and rapid response, followed by the complete resolution of the lesions in about 15 days.

Unfortunately, the patient has subsequently experienced new episodes which, although always responding to therapy, have shown a relapsing course. This confirms the association between the dermatosis of our patient and the underlying lymphoproliferative disease, which our haematology colleagues have considered best left untreated.

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