Wells syndrome associated with chronic lymphocytic leukemia*

Petra Maria de Oliveira Duarte Stuhr[1] Everton Carlos Siviero do Vale[1]

DOI: http://dx.doi.org/10.1590/abd1806-4841.20153212

Abstract: Eosinophilic cellulitis or Wells syndrome is an uncommon skin condition of unknown etiology that can occur alone or associated with other conditions. Typically, it presents with recurrent pruritic, erythematous and edematous plaques, but it can also show clinical polymorphism. Besides the cutaneous lesions, patients can experience systemic manifestations like fever, malaise, arthralgia and peripheral blood eosinophilia. We describe a case of this rare syndrome that presented with polymorphic cutaneous lesions associated with a serious systemic disease, which was revealed through the investigation of the cutaneous disease.

Keywords: Cellulitis/diagnosis; Eosinophilia; Leukemia/complications; Skin manifestations

INTRODUCTION

Eosinophilic cellulitis, first described by Wells in 1971 as recurrent granulomatous dermatitis with eosinophilia, also known as Wells Syndrome (WS), is a rare inflammatory dermatosis observed in all age groups, without preference for gender and race.[1,2]

Its causes are not completely understood, but some authors believe it may be a local hypersensitivity reaction triggered by different factors such as insect bites, vaccines containing thimerosal, immunobiological medications, viral infections and parasitic infestations, among others. It may occur as an isolated condition or associated with other diseases, with sporadic reports of familial cases.[1-5]

Although it may present a polymorphic clinical picture, recurrent pruritic, erythematous and edematous plaques are typical, affecting more frequently the trunk, face, arms and neck, that tend to regress with hyperpigmentation. [6,7] The lesions may be preceded by local pain and a burning sensation, associated with fever, malaise, arthralgia and liver function abnormalities, besides peripheral blood eosinophilia in up to 50% of cases.[2,5,7]

Laboratory evaluation of patients with suspected WS should include a complete blood cell count, metabolic panel, stool examination when intestinal parasitic infestation is suspected, and a cutaneous lesion biopsy.[2,5]

The histopathological examination may show three different stages. The acute phase is characterized by edema in superficial and middle dermis, with dense and diffuse eosinophilic inflammatory infiltrate. Eventually, the papillary dermal edema may be intense enough to result in cleavage and formation of subepidermal blisters. In the subacute or granulomatous phase it is possible to identify "flame figures" in the dermis, formed by collagen fibers covered by eosinophil granule proteins and surrounded by histiocytes and eosinophils. The regression phase exhibits gradual reduction of eosinophils, persistence of histiocytes and the appearance of giant cells around deposits of collagen, forming microgranulomas. None of the stages shows vasculitis.[3,6]

Received on 16.10.2013.
Approved by the Advisory Board and accepted for publication on 06.01.2014.
* Study carried out at the Dermatology Service of the Teaching Hospital of Universidade Federal de Minas Gerais (HC-UFMG) – Belo Horizonte (MG), Brazil.

Financial Support: None.
Conflict of Interest: None.

[1] Universidade Federal de Minas Gerais (UFMG) – Belo Horizonte (MG), Brazil.

CASE REPORT

A mestizo female 62-year-old patient, being treated for hypertension and without other comorbidities, had presented intensely pruritic lesions on the upper and lower limbs for 18 months, without identification of a triggering factor. During the dermatological examination, erythematous papular plaques were observed, some of them with superposition of serohemorrhagic vesicles and erosions located on limbs and back, besides papular purpuric lesions on the lower limbs (Figures 1 to 3). Cervical, supraclavicular and axillary hard and adherent lymphadenopathies could also be noticed (Figure 4).

The use of hydrochlorothiazide had been suspended after a prior cutaneous biopsy at another service, suggesting drug skin eruption, without improvement; prednisone 80mg per day was introduced, achieving only partial control of the clinical picture.

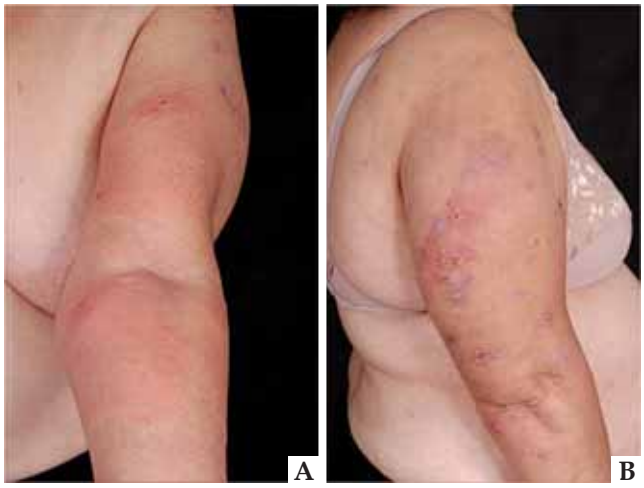

Figure 1 A: Diffuse erythema and edema, with numerous microvesicles; **B -** Papules and plaques, vesicles and erosions isolated and in groups

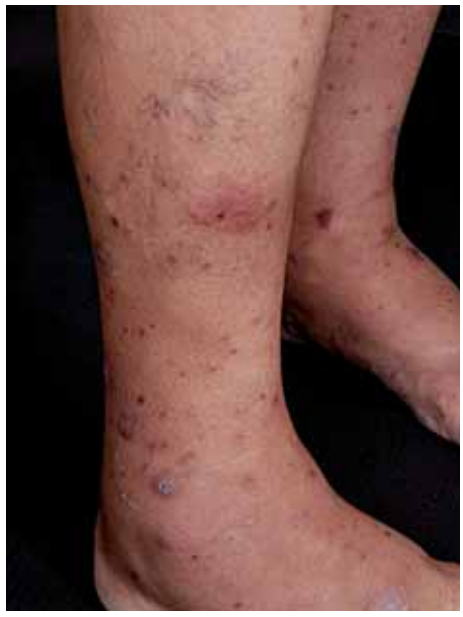

Figure 3: Papular purpuric lesions on the legs

The hypotheses of dermatitis herpetiformis, linear IgA bullous dermatosis, leukocytoclastic vasculitis, Sweet's syndrome and probable systemic lymphoma were considered and a cutaneous biopsy was performed for histological examination and direct immunofluorescence (DIF). A laboratory review and interconsultation with hematology were requested and an antihistamine was started for pruritus control.

During follow-up, the patient maintained periods of remission and exacerbation of the cutaneous clinical picture. After lymph node biopsy, the chronic lymphocytic leukemia diagnosis was confirmed by

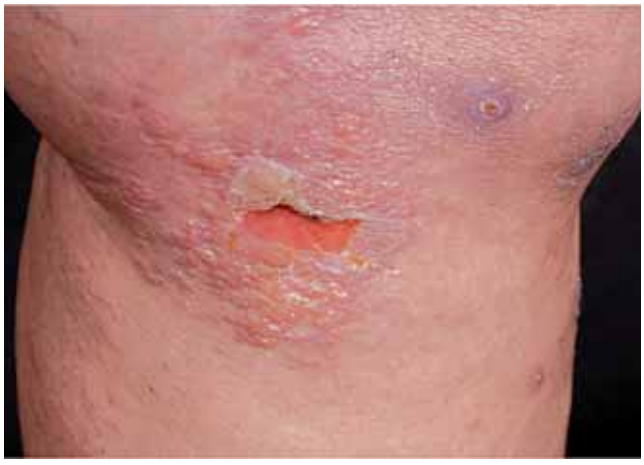

Figure 2: Diffuse erythema and confluent vesicles with central erosion on lower limb

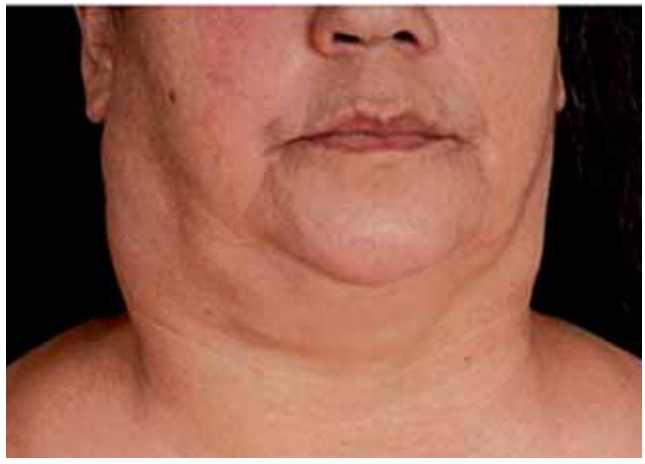

Figure 4: Cervical and supraclavicular masses

the hematology team.

The histopathologic examination showed hyperkeratosis, acanthosis, papillary dermal edema with cleavage and subepidermal blisters; a moderate, lymphohistiocytic and eosinophilic diffuse dermal inflammatory infiltrate, extending to the hypodermis, besides the typical "flame figures" in the middle and deep dermis (Figures 5 and 6). DIF was negative and the immunohistochemical examination ruled out neoplastic skin infiltration.

The clinical and pathological correlation allowed the WS diagnosis, with complete resolution of the cutaneous clinical picture after chemotherapy for leukemia treatment.

DISCUSSION

With a polymorphic clinical presentation and relative rarity, WS is a diagnostic challenge for the dermatologist. It should always be considered in cases with a diagnosis of bacterial cellulitis which do not respond to antibiotic therapy. Another important differential diagnosis is the hypereosinophilic syndrome (HES), a multisystemic disease that may be fatal and presents persistent eosinophilia in peripheral blood, in addition to the involvement of internal organs.[5]

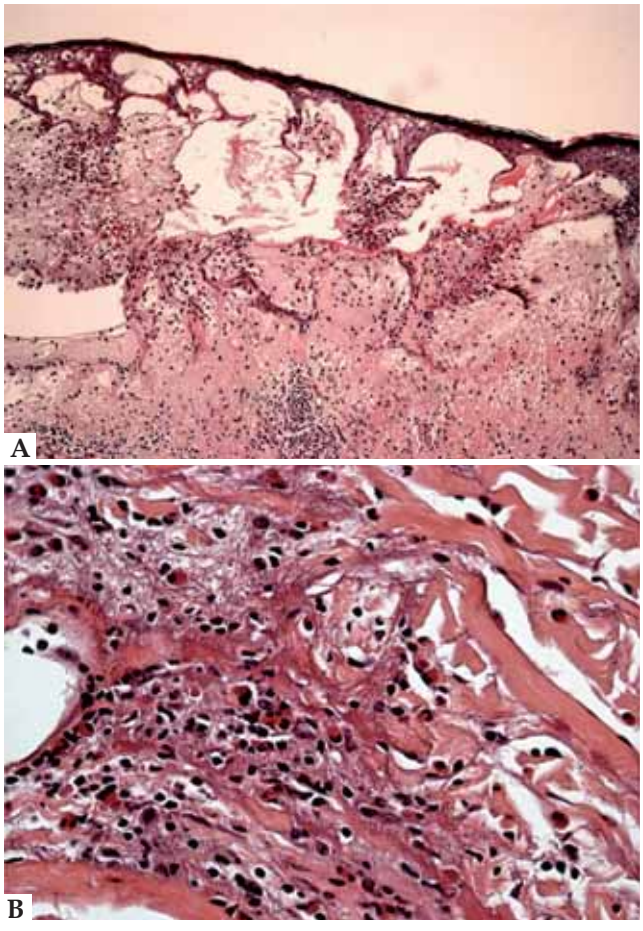

Figure 5A: Papillary dermal edema, leading to formation of extensive subepidermal blisters and diffuse dermal inflammatory infiltrate (HE 100x); **B -** Detail of inflammatory infiltrate, rich in eosinophils (HE 400x)

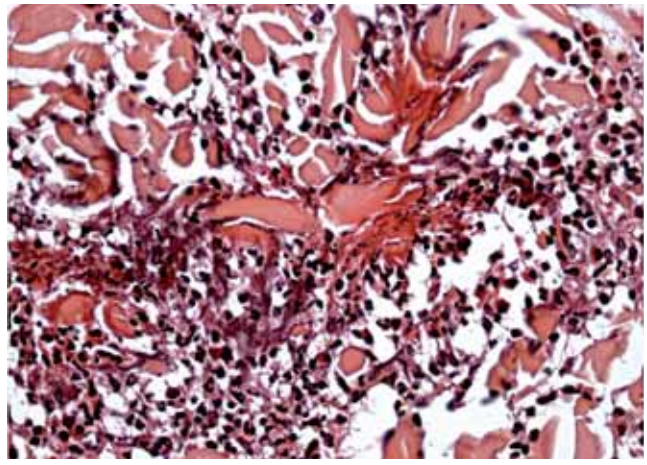

Figure 6: Typical flame figure, showing degenerated collagen fibers surrounded by histiocyte and eosinophil infiltrate (HE 400x)

Other differential diagnoses, mainly due to the histological similarity of the inflammatory infiltrate rich in eosinophils, are reactions to drugs, Churg-Strauss syndrome (CSS) and bullous pemphigoid, the latter especially important in cases with subepidermal blisters. In both CSS and WS there may be eosinophilia, increased IgE levels, increased eosinophil cationic protein, in addition to "flame figures" and formation of granulomas at the histopathological examination; what differentiates the two syndromes histologically is necrotizing vasculitis of small and middle vessels present in CSS, besides clinical findings such as sinusitis, asthma, mononeuritis and pulmonary infiltration. Some authors believe that WS, CSS and HES are part of the spectrum of eosinophilic disorders; therefore, they suggest that patients with WS be investigated and periodically monitored due to the risk of developing CSS and HES.[3,8]

The histopathologic finding of "flame figures" is typical of the disease, although unspecific. They can be observed in arthropod bites, parasitic infestations and drug reactions. Leiferman et al consider their presence mandatory for a WS diagnosis. [9]

It is believed that this syndrome is a local hypersensitivity reaction triggered by different factors. Although the pathogenesis is still not completely understood, there is evidence that interleukin 5 production is increased, which would be responsible

for migration of eosinophils from the bone marrow to the skin and their degranulation, resulting in tissue damage. The activated eosinophils apparently also secrete eosinophil cationic protein, a ribonuclease that is toxic for bacteria and helminths, which might contribute to the skin lesion.

In view of the diversity of triggering factors and possible association with severe diseases like lymphoproliferative disorders, systemic vasculitides and neoplasms, a thorough clinical evaluation of the patients becomes mandatory.[3,7,10]

In general corticotherapy allows good control of cases of isolated syndrome[1] with prednisone in a 10-60mg/day dose, but the cases associated with other conditions are most often resolved only with treatment for the basic disease. Other treatments described are ciclosporin, azatioprin, dapsone and tacrolimus. A spontaneous resolution of the clinical picture is also possible.[1,7,10] ❑

REFERENCES

1. Moossavi M, Mehregan DR. Wells' syndrome: a clinical and histopathologic review of seven cases. Int J Dermatol. 2003;42:62-7.
2. Powell JG, Ramsdell A, Rothman IL. Eosinophilic cellulitis (Wells syndrome) in a pediatric patient: a case report and review of the literature. Cutis. 2012;89:191-4.
3. Ratzinger G, Zankl J, Zelger B. Wells syndrome and its relationship to Churg-Strauss syndrome. Int J Dermatol. 2013;52:949-54.
4. Boura P, Sarantopoulos A, Lefaki I, Skendros P, Papadopoulos P. Eosinophilic cellulitis (Wells' syndrome) as a cutaneous reaction to the administration of adalimumab. Ann Rheum Dis. 2006;65:839-40.
5. Maiberger M, Maher I. JAAD Grand Rounds quiz. Pruritic, recurrent, erythematous plaques. J Am Acad Dermatol. 2011;64: 214-6.
6. Caputo R, Marzano AV, Vezzoli P, Lunardon L. Wells syndrome in adults and children: a report of 19 cases. Arch Dermatol. 2006;142:1157-61.
7. Spinelli M, Frigerio E, Cozzi A, Garutti C, Garavaglia MC, Altomare G. Bullous Wells' syndrome associated with non-Hodgkin's lymphocytic lymphoma. Acta Derm Venereol. 2008;88:530-1.
8. Gleich GJ, Leiferman KM. The hypereosinophilic syndromes: current concepts and treatments. Br J Haematol. 2009;145:271-85.
9. Leiferman KM, Peters MS. Reflections on eosinophils and flame figures. Arch Dermatol. 2006;142:1215-8.
10. Nakazato S, Fujita Y, Hamade Y, Nemoto-Hasebe I, Sugita J, Nishie W, et al. Wells' syndrome associated with chronic myeloid leukaemia. Acta Derm Venereol. 2013;93:375-6.

Mailing address:
Petra Maria de Oliveira Duarte Stuhr
Alameda Alvaro Celso 55
Santa Efigênia
30150-260 Belo Horizonte, MG.
E-mail: petraduarte@yahoo.com.br

How to cite this article: Stuhr PMOD, Vale ECS. Wells syndrome associated with chronic lymphocytic leukemia. An Bras Dermatol. 2015;90(4):571-4