

# Wells Syndrome with Multiorgan Involvement Mimicking Hypereosinophilic Syndrome

M. Carlesimo<sup>a</sup> L. Fidanza<sup>a</sup> E. Mari<sup>a</sup> G. Feliziani<sup>a</sup>  
A. Narcisi<sup>a</sup> G. De Marco<sup>a</sup> A. Bartolazzi<sup>b</sup> G. Camplone<sup>a</sup>

<sup>a</sup>U.O.C. Dermatology and <sup>b</sup>Histopathology, II Unit University of Rome 'Sapienza', Rome, Italy

## Key Words

Wells syndrome · Hypereosinophilic syndrome · Parotid gland · Eosinophil-associated diseases · Flame figures

## Abstract

Eosinophil-associated diseases represent a spectrum of heterogeneous disorders, where blood and cutaneous eosinophilia is the most important feature and eosinophils are the principal cause of cutaneous lesions. These diseases show some similarities in the clinical features but also many distinctive characteristics [Saurat et al., *Dermatologia e malattie sessualmente trasmesse*, Milano, Masson, 2000]. Wells syndrome is one of these disorders and is an uncommon recurrent inflammatory dermatosis, rarely associated to signs and symptoms of multiple organ involvement [Arch Dermatol 2006;142:1157–1161]. Hypereosinophilic syndrome, in contrast, constitutes a group of idiopathic disorders characterized by blood eosinophilia for at least 6 months, associated with single or multiple organ system dysfunction [Arch Dermatol 2006;142:1157–1161]. Clinically atypical Wells syndrome with multiorgan involvement is reported here. A correct diagnosis is difficult in this case, but clinical and histopathological features are compatible with this diagnosis. The reported condition likely represents a borderline hypereosinophilic disease, in which clinical features of both hypereosinophilic syndrome and Wells syndrome are present.

## Introduction

Wells syndrome is an uncommon recurrent inflammatory dermatosis of unknown aetiology with distinctive but unspecific histopathological features and clinical polymorphism [1]. It is characterized in most cases by large erythematous and

oedematous plaques of annular or circinate morphology, resolving without any outcome [2]. Histopathological findings consist of dermal eosinophilic infiltration and ‘flame figures’, an aggregation of eosinophils among the dermal collagen bundles. This condition is rarely associated with systemic involvement, but peripheral blood eosinophilia is common [3]. The course of this dermatosis may be subacute for months or years, with complete resolution, and possible recurrence after long periods [2].

In contrast, hypereosinophilic syndrome (HES) constitutes a group of idiopathic disorders associated with multiple organ dysfunction, sometimes fatal. The criteria of diagnosis are: persistent idiopathic blood eosinophilia, at least for 6 months; signs or symptoms of organ involvement (haematological, cardiac, pulmonary, rheumatological, gastrointestinal, musculoskeletal, neurological disorders) [4]. Cutaneous manifestations are pruritic or erythematous papules, plaques and nodules, with urticaria and angio-oedema, present in more than half of the cases [3, 4]. Histopathological findings are unspecific with variable dermal infiltration of mixed inflammatory cells, including eosinophils, without evidence of flame figures, because there is insufficient degranulation of eosinophils in the skin [1].

Herein we report a case that showed clinical features of Wells syndrome, but was associated with a diversity of systemic signs and symptoms (parotid glands, pancreas and lungs).

### Case Report

A 69-year-old man was referred to our department in February 2007 with pruritic erythematous and oedematous plaques, papulovesicular lesions and some large blisters particularly localised on the trunk and extremities. The patient showed marked bilateral parotid enlargement with involvement of the face, neck and upper surface of the trunk. The submandibular lymph nodes were swelled. Dermatological features consisted of erythematous lesions that were observed on the upper legs (fig. 1). General symptoms were fever (38–39°C) and fatigue. His initial blood count showed a white cell count  $12.3 \times 10^6/l$  with 31.5% eosinophils and 15.7% lymphocytes. Nevertheless stool was negative for ova and parasites, no viral infection was demonstrated, there was no evidence of allergic disease or eosinophilic leukemia. We also investigated the hypothesis that constitutional genetic variation in IL-5 signalling might be involved in this condition, but the results of the molecular analysis were negative, bone marrow tests were negative, and there was not evidence of monoclonal T-cell population. Other laboratory exams were normal or negative, and serological tests, including the assays of the main autoantibodies, complement, circulating immunocomplexes and tumour markers were non-contributory. A skin biopsy specimen taken from the site of oedematous erythema on the left upper leg revealed, at histology, a diffuse and heavy infiltrate of eosinophils in the dermis with extension into the underlying subcutaneous tissue.

Treatment with intravenous corticosteroids (betamethasone 4 mg/day) was finally started, but the levels of eosinophils fluctuated with the course of the disease, reaching a maximum of 5,400/ $\mu$ l and, at the same time, amylase levels increased to 256 U/l (normal 8–53 U/l) and lipase levels to 2,400 U/l (normal 20–300 U/l). Therefore, instrumental investigations were made: abdominal ultrasound did not show any relevant alteration in the liver and spleen, and chest X-ray and echocardiography were in the normal range. Total body computerized tomography finally showed a marked bilateral enlargement of the parotid and submandibular glands, the presence of a little pancreas enlargement and a pulmonary embolism, supported by increased D-dimer levels (800 mg/l).

Typical clinical picture, negative IMF, absence of associated immunomediated systemic diseases, and blood eosinophilia suggested that, in spite of the absence of flame figures, not present in every stage of Wells eosinophilic cellulitis, the case could be classified as Wells syndrome. Anticoagulant therapy was started (heparin s.c. 8,000 IU/day) associated with corticosteroid therapy with methylprednisolone (16 mg/day). After a month of therapy, in which the steroid dose was gradually tapered, we observed complete clearance of the skin lesions and normalization of blood eosinophil count and pancreatic enzymes (amylase and lipase) levels.

## Discussion

Wells syndrome (or eosinophilic cellulitis) was first described by Georg Crichton Wells in 1971, who named it ‘recurrent granulomatous dermatitis with eosinophilia’; in 1979 this definition was modified to ‘eosinophilic cellulitis’ or ‘Wells syndrome’ [1]. Clinically, in most cases, it is characterized by annular or circinate erythematous-oedematous plaques, but a wide variety of clinical pictures have been described, including blistering, nodules, papulovesicular eruptions and excoriated papules [5]. It is considered as a distinct entity, and seven clinical variants of this disease are described: plaque-type, annular granuloma-like, urticaria-like, papulovesicular, bullous, papulonodular and fixed drug eruption-like [5]. Histopathological features can be categorized into three different phases: acute, subacute and regressive. The acute phase is characterized by oedema of superficial dermis and middermis with eosinophilic infiltrate; in the subacute phase flame figures in the dermis can be noted, consisting of eosinophilic major basic protein deposited on collagen bundles and widespread degranulation of eosinophils; the regressive phase, instead, is characterized by disappearance of eosinophils with persistence of histiocytes and microgranulomas composed of giant cells, deposited around collagen deposits [1]. Flame figures are an important histological feature of Wells syndrome, but are not present in every phase and are not pathognomonic of this disease; in fact, they can be associated with other dermatologic conditions such as pemphigoid, eczema, prurigo, tinea infection, herpes gestationis, cutaneous mastocytoma and scabies [2, 6, 7]. The course of this condition is almost invariably benign, with episodic remissions and relapses.

HES is an idiopathic condition characterized by persistent eosinophilia for at least 6 months, with involvement of one or more organs. The heart, lungs, nervous system, liver and skin are commonly affected [8]. Diagnosis of this disease always requires a careful exclusion of other pathological conditions in which eosinophilia is present, in particular parasitic infection; it has been also reported in association with systemic diseases such as T-cell lymphoma, mast cell disease and HIV infection [4, 9]. Cutaneous lesions are present in about 50% of patients and usually consist of pruritic papules and nodules, or urticaria and angioedema. Oral and genital erosions are quite characteristic and may be the first manifestation of the disease [10]. Recently three types have been characterized: myeloproliferative HES, lymphocytic HES and other heterogeneous clinical conditions (unclassified HES). Myeloproliferative HES can be differentiated by eosinophilic leukemia for the presence of mature eosinophils and for absence of clonal expansion. Lymphocytic HES is characterized by T-cell clonality, in particular CD3+CD4–CD8– and CD3–CD4+. This disease presents, in general, a benign course, but some patients can develop a lymphoma. The term ‘unclassified HES’ includes different entities, such as Gleich syndrome (episodic angioedema and eosinophilia) and NERDS (disseminated nodules, eosinophilia, rheumatism and dermatitis), that present also a T-cell clonality. Recent advances in the pathogenesis of this condition have established that hypereosinophilia may be triggered either by a primitive involvement of myeloid cells due to the occurrence of an interstitial chromosomal deletion on 4q12, which generates a *FIP1L1-PDGFR*A fusion gene (F/P<sup>+</sup> variant), or by an increased IL-5 production that follows a clonal expansion of the T-cell population (lymphocytic variant), most frequently characterized by a CD3–CD4+ phenotype [10].

The association of Wells syndrome and HES has occasionally been reported. Heterogeneity of symptoms and association with other diseases led to doubted the identity of Wells syndrome. Aberer et al. [7], in 1988, postulated that it might be considered as a distinctive entity and not only as a clinical and histological reaction to

several conditions. In contrast, other authors postulated that this syndrome could be considered as a cutaneous manifestation of HES [1, 3]. In fact, clinical and histopathological findings of both syndromes may overlap, suggesting that this condition may represent, at least for some patients, the benign evolution of HES [4].

In our patient we could exclude the diagnosis of HES because of the absence of persistent eosinophilia, of clinical features and of molecular alterations typical of this syndrome. However, we could support the diagnosis of Wells syndrome. Wells syndrome and HES, at least in some of the cases, should be considered as part of a spectrum of hypereosinophilic disorders triggered by causative agents that include insect bites, arthropod bites, onchocerciasis, varicella, mumps, drug reactions, atopic diathesis, fungal infection, carcinomas, haematological diseases and eosinophilic myositis [2, 11–14]. In the literature there are few cases of Wells syndrome associated with haematological malignancies and cases with underlying nonhaematological malignancies (squamous cell carcinoma, nasopharyngeal carcinoma and colon carcinoma) or liver involvement reported [15, 16], but none with a simultaneous involvement of the parotid glands and the pancreas or pulmonary embolism.

In our opinion, in the next future molecular and immunological studies, directed to better understand the pathophysiology of nonneoplastic eosinophilic proliferation, will contribute to better clarify the nosological classification of these intriguing pathological conditions.

**Fig. 1.** **a** Marked bilateral parotid enlargement on the face and neck. **b** Erythematous lesions of the upper leg.



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All authors contributed equally to this report.