

Report

Wells syndrome and its relationship to Churg–Strauss syndrome

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Abstract

Background Wells syndrome has been described as an inflammatory disorder based on typical clinical appearance combined with the histopathological presence of eosinophilic infiltrates and flame figures in the absence of vasculitis. Churg–Strauss syndrome, on the other hand, is primarily a diffuse, necrotizing vasculitis but is also typically displaying eosinophils and flame figures. Despite several parallels, the present understanding of these two diseases excludes any pathogenetic relationship.

Methods We describe the clinical course and histopathological appearance of three patients who had initially been diagnosed with Wells syndrome that developed into Churg–Strauss syndrome during the course of their disease.

Results The clinical presentation of all three patients led to the diagnosis of Wells syndrome by independent specialists. Histopathology showed an eosinophilic infiltrate and flame figures next to features of leukocytoclastic vasculitis. Detailed examination revealed asthma bronchiale and additional symptoms indicating Churg–Strauss syndrome. The initial diagnosis of Wells syndrome had to be revised to Churg–Strauss syndrome.

Conclusion We conclude that Wells syndrome could be the starting point of a pathogenetic process that might reach its maximum in Churg–Strauss syndrome. As a clinical consequence, patients with Wells syndrome should be evaluated and followed for Churg–Strauss syndrome.

Introduction

Wells syndrome

Wells syndrome (WS) has been defined as a typical clinical and histopathological entity. Since the pioneering work of G.C. Wells¹ in 1971, the clinical appearance has been described as a first phase of localized redness and edema (eosinophilic cellulitis) followed by a second phase of indurated, slate-colored plaques (granulomatous dermatitis). Histopathologically, the definition of the syndrome describes three stages: (i) an acute stage of eosinophilic cellulitis with subepidermal edema and masses of eosinophils throughout the dermis; (ii) a subacute stage of granulomatous dermatitis with typical flame figures; and (iii) a final stage of resolution.^{1–4} The so-called flame figures are caused by degranulating eosinophils covering collagen fibers with eosinophilic major basic protein⁵ and fibrin. Restoration is introduced by the appearance of macrophages palisading around these flame figures. Approximately 50% of patients show peripheral blood eosinophilia during active disease. Furthermore, increased eosinophilic cationic protein and interleukin-5

have been detected in peripheral blood.⁶ No evidence of vasculitis has been described at any stage of the disease so far.^{1–4}

Churg–Strauss syndrome

Churg–Strauss syndrome (CS) is primarily a diffuse, necrotizing, eosinophilic vasculitis that can nearly affect all major organ systems.⁷ Three distinct clinical phases are distinguished, namely an allergic, eosinophilic, and vasculitic phase. The latter, especially when affecting several organ systems, can possibly lead to a lethal outcome. The dermatological features are variable, including palpable purpura and erythematous, maculopapular, and pustular lesions as well as nodules on the head, trunk, and extremities. Histopathologically, there is a pronounced perivascular inflammatory infiltrate dominated by eosinophils, but also macrophages and lymphocytes that pervade the vessel wall of arterioles, venules, and capillaries. Flame figures caused by degranulating eosinophils are also a typical feature. The strong inflammation leads to fibrinoid necrosis in medium to small-sized vessels and subsequently to necrosis within the connective tissue with characteristic granuloma forma-

tion. Asthma and atopy are closely linked with CS, and both are associated with blood eosinophilia. Approximately 50% of patients develop antineutrophil cytoplasmic antibodies (ANCA) that can amplify inflammation by neutrophil activation and degranulation, although they are not viewed as the primary cause of the disease. Further, one can find elevated IgE, eosinophilic cationic protein, soluble interleukin-2 receptor, and soluble thrombomodulin. The American College of Rheumatology (ACR) has established six criteria for the classification of CS: asthma bronchiale, peripheral eosinophilia (>10%), paranasal sinusitis, pulmonary infiltration, histological evidence of vasculitis, and mononeuropathy. The presence of four or more of these criteria has a sensitivity of 85% and specificity of 99.7% for CS.⁶

Wells syndrome vs. Churg–Strauss syndrome

Eosinophilic granulocytes in combination with flame figures were originally described as a hallmark for WS. However, they are not exclusive or pathognomonic.^{7,8} They have also been described in a variety of other diseases, including insect bites,^{9,10} autoimmune bullous dermatoses,¹¹ parasite/dermatophyte infections,^{12–16} viral infections,¹⁷ as a reaction to the administration of thiomersal-containing vaccines¹⁸ as well as adalimumab¹⁹ and etanercept,²⁰ and associated with hypereosinophilic syndrome.^{21,22} Most importantly, however, they are also regularly found in CS.²³ Furthermore, WS and CS share elevated IgE, blood eosinophilia, elevated eosinophilic cationic protein, tissue eosinophilia, and the formation of granulomas in later stages. The differences mainly concern the appearance of vasculitis. While Churg and Strauss²³ described the syndrome as a necrotizing vasculitis of medium-to-small-sized blood vessels, vasculitis *per se* has been excluded per definition from the diagnosis of

WS. Thus, the present understanding of these two diseases excludes any pathogenetic relationship.

We present three patients with a clinicopathological overlap of these syndromes. On the one hand, we detected vasculitic signs in typical clinical presentations of WS and on the other rather subtle signs of vasculitis in CS.

Our objectives are to discuss whether WS could be part of a broader entity of eosinophilic dermatosis and whether it could be considered as an early form or prodromal manifestation of CS.

Methods

Three patients with both WS and CS granulomatosis in their disease course were re-evaluated. Cases were retrieved between 2002 and 2007 (Table 1).

Routine hematoxylin/eosin staining and periodic acid-Schiff staining were performed on formalin-fixed, paraffin-embedded biopsies. Four-micrometer thick sections of all cases were examined to evaluate the following histopathological features: inflammatory infiltrate (+: light, mainly perivascular, and moderately interstitial infiltrate; ++: intense nodular to diffuse infiltrate); subepidermal edema (+: mild edema; ++: strong edema); eosinophils and flame figures; lymphocytes, as well as vasculitic features (Table 2). We defined vasculitis histologically with: (i) the presence of erythrocyte extravasates; (ii) nuclear dust; (iii) fibrin in or around vessel walls; and/or (iv) collagen degeneration in a perivascular, neutrophil-containing inflammatory infiltrate (+: mild; ++: strong).

Cases and results

Patient 1

A 9-year-old girl presented with urticarial lesions on her face, neck, upper arms, and back in March 2003

Table 1 Demographic and clinical data

Patient no.	Sex	Age (years) at time of diagnosis	Histopathologic diagnosis	Final diagnosis	Clinical history	Therapy	Course	Peripheral eosinophilia
1	F	9	WS, CS	CS	Asthma Eosinophilia Vasculitis	Methylprednisolone	Cured after one episode	+
2	F	39	WS, CS	CS	Asthma Eosinophilia Sinusitis Organ involvement (lung, kidney) Allergies	Methylprednisolone Cyclophosphamide	Stable disease with intermittent flare-ups	+
3	M	52	WS, CS	CS	Asthma Sinusitis Vasculitis	Methylprednisone	Ongoing	+

F, female; M, male; +, positive.

Table 2 Histopathologic features

Patient	Infiltrate	Edema	Neutrophils	Eosinophils	Erythrocytes	Lymphocytes	Nuclear dust	Fibrin ^a	Collagen	Flame figures
1	++	–	++	++	–	+	+	–	+	++
2	+	+	+	++	–	+	+	+	–	++
3	+	–	+	++	–	+	++	–	+	++

–, negative; +, positive; ++, strongly positive.

^aFibrin in or around vessel walls.

(Fig. 1a,b). She reported that itchy lesions had been present for weeks, and she could not recall any insect bites. Clinically, erythematous, edematous plaques with partial

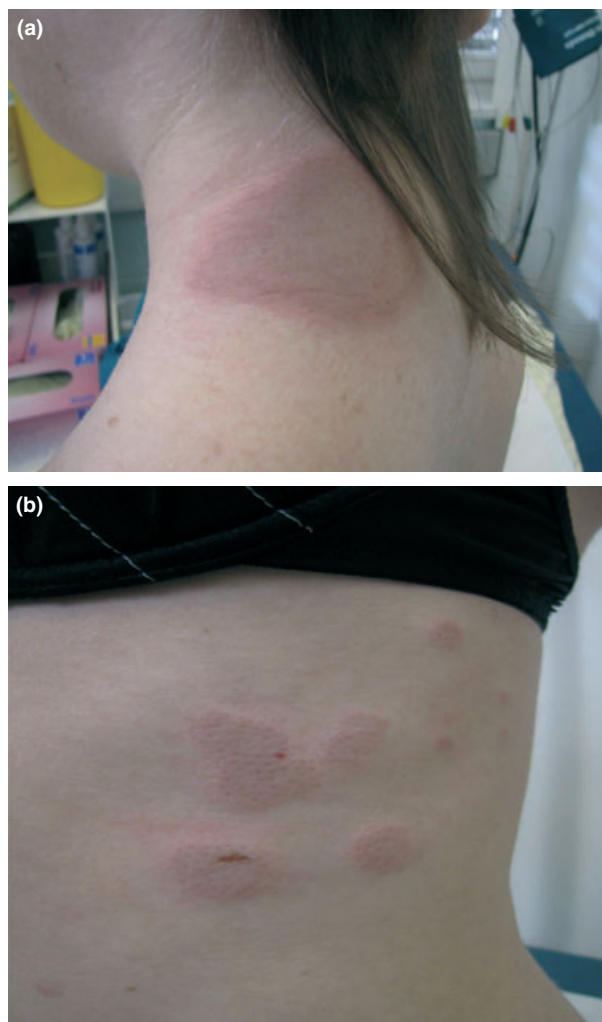


Figure 1 (a) Erythematous plaque with central clearing on the neck of a 9-year-old girl. (b) Multiple erythematous round to polycyclic plaques with signs of mechanical irritation on the back of a 9-year-old girl

central clearing and partial signs of scratching were found. WS was clinically suggested and a biopsy taken. Histopathology showed a perivascular eosinophilic infiltrate as well as flame figures next to neutrophils, nuclear dust, and interstitial degeneration of collagen and was primarily interpreted as WS (Fig. 2a,b). The girl was admitted and thoroughly examined. Allergic asthma bronchiale, peripheral eosinophilia >10%, and elevated IgE were found; however, no further involvement of inner organs could be shown. ANCA were negative. The synopsis of clinical and histopathological findings finally led to the diagnosis of incipient CS (three ACR criteria). The girl was treated with systemic corticosteroids with permanent clearing of the cutaneous lesions, while the respiratory symptoms still required therapy.

Patient 2

In November 2002, a 39-year-old woman presented with erythematous papules and plaques accentuated in the armpits and buttocks. The lesions had appeared eight days before and were hot and itchy. They showed centrifugal growth with formation of figurated lesions and accentuation of the outer rim. Initially, insect bites were suggested. The development of the lesions and their later appearance led to modification of the clinical diagnosis to WS. Histopathology (Fig. 3a–c) showed an interstitial eosinophilic infiltrate and flame figures next to neutrophils and mild fibrin in and around vessel walls without, however, further signs of vasculitis or granulomas. WS was proposed, but an early form of CS was also discussed. Further medical history revealed asthma bronchiale for 20 years, pansinusitis, recurrent swelling of joints, and multiple allergies. Laboratory tests showed peripheral eosinophilia >10%, elevated IgE, elevated eosinophilic cationic protein, and proteinuria. ANCA was negative. Examination of inner organs revealed granulomas in lungs and kidneys. Finally, the diagnosis was changed into CS (four ACR criteria). The patient underwent surgery for pansinusitis and was additionally treated with corticosteroids and cyclophosphamide with partial success and regular flare-ups to this date.

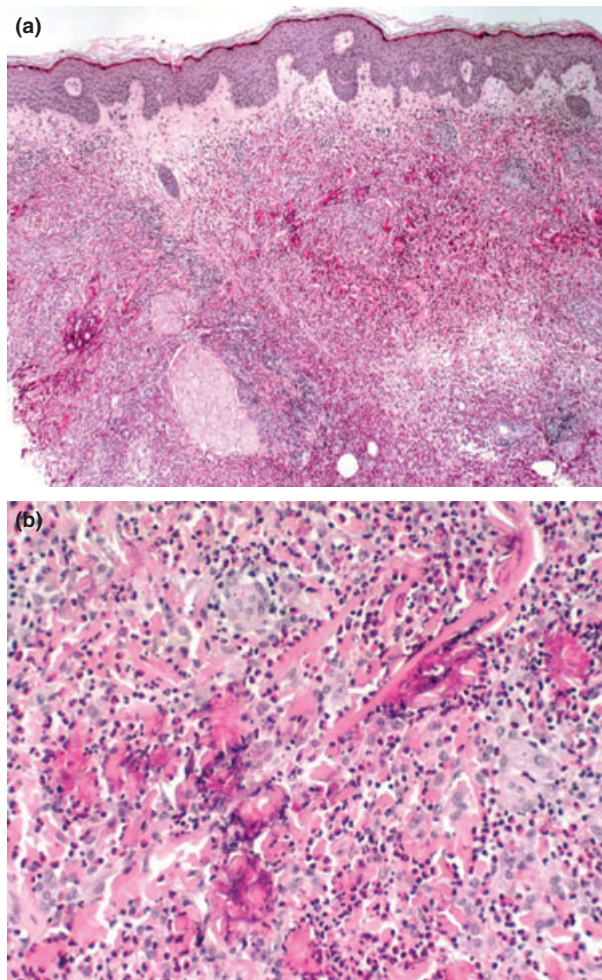


Figure 2 (a) Subepidermal edema, perivascular, nodular to diffuse eosinophilic infiltrate (hematoxylin and eosin, $\times 10$). (b) Infiltrate rich in eosinophils, nuclear dust, flame figures, degenerated collagen, and some macrophages (hematoxylin and eosin, $\times 40$)

Patient 3

In 2007, a 52-year-old man presented with recurrent urticarial plaques compatible with the clinical diagnosis of urticaria, panniculitis, or WS. Histopathology showed neutrophils and eosinophils around postcapillary venules as well as flame figures and collagen degeneration next to prominent nuclear dust. Although WS was diagnosed, early CS granulomatosis was additionally considered. Clinical examination revealed asthma, chronic paranasal sinusitis, hyper-IgE, and mild peripheral eosinophilia ($<10\%$). ANCA were negative. No further organ involvement could be verified. Incipient CS was diagnosed (three criteria) and successfully treated with corticosteroids. No further flare-ups of the skin manifestations were reported, and the patient is still under anti-asthmatic treatment as he had been before the appearance of the cutaneous lesions.

Discussion

WS or eosinophilic cellulitis is a rare inflammatory disorder of unknown etiology. In 1971, Wells described four patients with a dermatosis he called “recurrent granulomatous dermatitis with eosinophilia.”¹ In 1979, Wells and Smith² added another eight patients and modified the name to “eosinophilic cellulitis,” defining a distinctive clinical and histopathological entity. In the same year, Spigel and Winkelmann introduced the term WS.³ The presence of an eosinophil-dominated infiltrate and flame figures in the absence of vasculitis have been considered typical, defining a unique clinicopathological entity.^{1–4} The pathogenesis of the disease remains unclear, and various associations with hematologic disorders, infections, drugs, surgery, and solid neoplasms have been reported.^{24,25}

Conflicting views as to whether WS exists as an independent entity or not have been repeatedly expressed. Aberer *et al.*²⁶ describe it as a distinctive dermatosis with characteristic histopathology and typical clinical picture and course. Odom *et al.*²⁷, on the other hand, do not see it as a distinct entity but as a reaction pattern to many possible allergic stimuli. Bogenrieder *et al.*²² favor the hypothesis that WS and hypereosinophilic syndrome represent an abnormal eosinophilic response to a variety of underlying diseases or causative agents and thus are different expressions of one entity linked to the immunobiology of eosinophils. Ackerman *et al.*²⁸, on the other hand, see it as “nothing more than a histopathological pattern accompanying findings of very different diseases that have in common dense infiltrates of eosinophils, degranulation of which leads to formation of flame figures, which in turn induce a foreign-body granulomatous response.”

All three patients had been referred to our department with the clinical suspicion of WS. In all three cases, experienced dermatologists from other clinical departments (patient 1 from Frankfurt and patient 2 from Münster, both Germany) or from private practice (patient 3) as well as us have clinically diagnosed WS. Upon further examination, patient 1 showed vasculitis on biopsy as well as asthma bronchiale and peripheral eosinophilia. The combination of these three criteria is highly suggestive for CS, although it is not a classic disease of childhood.²⁹ Patient 2 was found to have widespread disease with involvement of lungs and kidney next to asthma bronchiale, pansinusitis, and eosinophilia (four criteria). Interestingly, she lacked definite signs of vasculitis in her biopsy (only discrete fibrin in and around vessel walls). Patient 3 showed vasculitic features on biopsy next to asthma bronchiale, paranasal sinusitis, and mild eosinophilia ($<10\%$) (three criteria). Incipient CS indicated itself. Unfortunately, ANCA were negative in all our patients. ANCA are usually present in 50–60% of patients with CS and would have helped our diagnosis his-

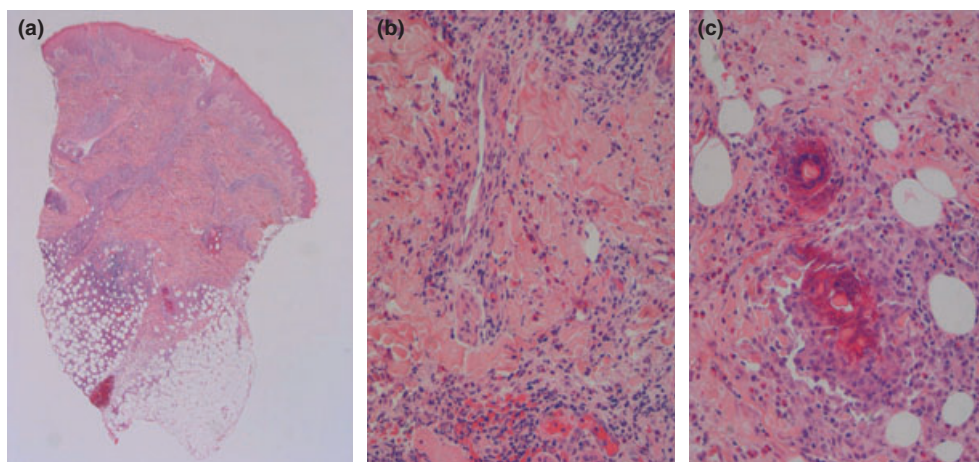


Figure 3 (a) Mild subepidermal edema, prominent perivascular nodular to diffuse infiltrate (hematoxylin and eosin [HE], $\times 10$). (b) Perivascular infiltrate consisting of eosinophils, neutrophils, and nuclear dust (HE, $\times 40$). (c) Flame figures with palisading macrophages (HE, $\times 40$)

tologically. For the sake of completeness, we cannot fully exclude the possibility of a mistake in the initial clinical diagnoses of WS, which was potentially secondary to sampling an area of skin that did not show significant leukocytoclastic vasculitis.

All our patients showed features of both WS and CS. The true diagnosis probably lies in-between the two entities. The eosinophilic infiltrate is the reflection of systemic disease. WS can appear as the prodromal manifestation of CS. In our opinion, such cases support the hypothesis that rare cases of WS are closely related to CS and that the two diseases might be part of the same pathogenetic process.

Conclusion

Our cases seem to be hybrids between WS and CS. By being able to correlate the clinical and histopathological features, we are inclined to regard them as stages in a pathogenetic process, which could start as the prodromal stage at WS and might reach its maximum at the full presentation of CS. We believe that WS exists but within the broader spectrum of eosinophilic dermatosis. The fact that our patients began with WS and were finally diagnosed with CS underlines the close relationship between these two manifestations. The diagnosis of WS should not exclude the possibility of vasculitis and, in case of progression – CS. As a clinical consequence, patients with WS should be evaluated and followed for CS.

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