Idiopathic Hypereosinophilic Syndrome With Cutaneous Manifestations and Flame Figures: A Spectrum of Eosinophilic Dermatoses Whose Features Overlap With Wells’ Syndrome

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**Importance:** Wells syndrome (WS) (eosinophilic cellulitis) is an uncommon eosinophilic dermatitis that has been rarely described in association with, but distinct from, hypereosinophilic syndrome (HES).

**Observations:** We report a case of an eosinophilic dermatosis with flame figures in association with idiopathic HES, manifested by inflammatory myocarditis, asthma, and peripheral blood eosinophilia.

**Conclusions and Relevance:** The diagnoses of WS and HES, rather than being distinct findings, may represent 2 entities on a spectrum of hypereosinophilic diseases. The diagnosis of WS should be made with caution and should prompt a thorough investigation that includes a work-up for a systemic eosinophilic disorder.

**Key Words:** Wells’ syndrome, hypereosinophilic syndrome, eosinophilia, flame figures

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**INTRODUCTION**

Wells syndrome (WS) and hypereosinophilic syndrome (HES) are 2 diagnoses that have remained distinct in the literature. WS (eosinophilic cellulitis) is a rare eosinophilic dermatitis of unknown pathogenesis. Despite many clinical presentations, it most commonly resembles an acute infectious cellulitis unresponsive to antibiotics. Most patients present with peripheral eosinophilia and, at times, systemic symptoms, including fever, malaise, and arthralgias.1

Conversely, in HES, most patients also present with peripheral eosinophilia and systemic involvement and nonspecific cutaneous manifestations.2 Unlike WS, which has distinctive histopathologic findings, the morphologic features associated with HES are not well defined.2

We report a case of systemic eosinophilia consistent with HES, but with cutaneous manifestations reminiscent of WS. Our aim is to describe the spectrum of clinicopathologic findings associated with WS and HES.

**CASE REPORT**

A 40-year-old woman with a history of Charcot-Marie-Tooth disease, asthma, and polysubstance abuse presented with chest pain and shortness of breath. She originally reported a 2-month history of increased lethargy, weight loss, and night sweats. Initial laboratory work-up revealed leukocytosis [46.6 × 10^9/µL, normal (nml): 4.5–11 × 10^9/µL] predominantly composed of eosinophils (61%, nml: 0%–5%) as well as elevated troponins (6.22 ng/mL, nml: < 0.11 ng/mL) with tachycardia and lateral ST segment depression. A cardiac magnetic resonance imaging showed features of acute myocarditis. The patient was started on intravenous solumedrol 125 mg every 8 hours and oral metoprolol 100 mg twice a day for her severe hypereosinophilia and myocarditis. At the time of admission, the patient denied recent exposures to any drugs of abuse, and urine and serum toxicology screens were negative.

A bone marrow aspiration and biopsy was performed, which revealed hypercellular bone marrow (80%–90%) (expected 60%) with marked granulocytic hyperplasia, eosinophilia (58%), and mild multilineage dysplasia. The eosinophils demonstrated subtle atypical features, including low nuclear to cytoplasmic ratio, hypo- and hypersegmented nuclei, and heterogeneous distribution of granules (Fig. 1). Mutational analyses, including fluorescence in situ hybridization for *BCR–ABL1*, *FIPLI–PDGFRα*, and *PDGFRB–ETV6* fusion products, and polymerase chain reaction analysis for *JAK2 V617* mutation, were negative. Peripheral blood T-cell receptor -β gene rearrangement studies showed a polyclonal T-cell population. Further immunologic work-up revealed an elevated immunoglobulin G level (2290 mg/dL, nml: 600–1500 mg/dL) and slightly elevated immunoglobulin M (366 mg/dL, nml: 46–304 mg/dL). Additional laboratory findings included a normal appearance of mast cells, normal serum tryptase, normocytic, normochromic anemia (hemoglobin 9.7 mg/dL; nml: 12–16 mg/dL), elevated serum B12 levels (1463 pg/mL; nml: 211–911 pg/mL), and mildly elevated alanine aminotransferase (122 U/L, nml 9–48 U/L). An extensive work-up for malignancy, allergy, autoimmune disorders, including antinuclear antibody/antineutrophil cytoplasmic antibody, and infections from the Departments of *Dermatology, and †Pathology, Wexner Medical Center, The Ohio State University, Columbus, OH.

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Numerous eosinophils with dysplastic features
Marked interstitial dermal eosinophilia with infiltration of the dermis
Patient's trunk, demonstrating erythematous, irregular papular rash of WS
Skin biopsy showing a diffuse dermal infiltrate extending from the superficial papillary dermis into the deep reticular dermis

FIGURE 1. Numerous eosinophils with dysplastic features including hypo- and hypersegmented nuclei with abnormal distribution of granules (Wright-Giemsa, magnification x600).

FIGURE 2. Patient's trunk, demonstrating erythematous, irregular papular rash of WS.

FIGURE 3. Skin biopsy showing a diffuse dermal infiltrate extending from the superficial papillary dermis into the deep reticular dermis (hematoxylin and eosin, magnification x20).

FIGURE 4. Marked interstitial dermal eosinophilia with infiltration into piloerector muscles (hematoxylin and eosin, magnification x200).

DISCUSSION
WS, or eosinophilic cellulitis, was first described in 1971 by Wells as a recurrent granulomatous dermatitis with eosinophilia. Since its original description, WS has been further categorized according to its multiple cutaneous presentations and histopathologic findings. Caputo et al. recently proposed 7 clinical variants of WS: annular granuloma-like, bullous, fixed drug eruption-like, papulonodular, papulovesicular, plaque-type, and urticaria-like. Our patient developed scattered erythematous, irregularly shaped, mildly indurated, tender papules on her lower back and abdomen reminiscent of the papulonodular form of WS. Despite its numerous clinical appearances, the recurrent pattern of disease, peripheral eosinophilia (>50% of patients), and characteristic histopathologic findings are the most helpful criteria in establishing the diagnosis of WS.

Three histopathologic stages of WS have been described. In the acute stage, WS manifests as dermal edema with a mostly eosinophilic infiltrate. A subacute phase shows granulomatous changes and degeneration of collagen with formation of flame figures. Flame figures represent the coating of degenerating collagen fibers with major basic protein, released from degranulation of eosinophils. The resolution stage shows palisading histiocytes surrounding the flame figures with occasional necrobiotic, lymphocytes, and eosinophils. Other diagnoses that may demonstrate flame figures include Churg–Strauss syndrome (CSS), parasitic or fungal infections, herpes gestationis, arthropod bites, bullous pemphigoid, and follicular mucinosis (among others).
Extensive peri- and intravascular eosinophilia without diagnostic evidence of a vasculitis (hematoxylin and eosin, magnification, ×400).

The diagnostic criteria for idiopathic HES were first outlined in 1975 by Chusid et al. Three criteria were proposed: (1) persistent eosinophilia greater than 1500 eosinophils per cubic millimeter for more than 6 months; (2) no other apparent etiology for the eosinophilia (eg, parasitic infections and allergies); and (3) clinical manifestations of organ damage (eg, asthma, myocarditis, enteritis). Furthermore, HES has been divided into 3 types: myeloproliferative (M-HES), lymphocytic HES, and undefined HES. Unlike WS, HES does not have consistent histopathologic manifestations, and the location and density of the inflammatory infiltrate vary. A mixed inflammatory infiltrate including neutrophils, lymphocytes, and histiocytes has been described, in addition to dermal eosinophilia. Flame figures have been only rarely associated with HES; this is thought to be the result of insufficient eosinophil degranulation. Interestingly, both WS and HES have been associated with increased expression of CD25 on the surface of eosinophils and the presence of eosinophil extracellular DNA traps. Interleukin 2 enhances platelet-activating factor-stimulated release of eosinophil cationic protein from CD25-expressing eosinophils but not from CD25-negative eosinophils. Such a “priming” effect has previously been described for eosinophil hematopoietins. Patients with increased eosinophil surface CD25 expression are at higher risk of eosinophil degranulation and subsequent tissue damage when interleukin 2 is present at inflammatory sites.

Our patient presented with a significant peripheral eosinophilia and radiologic evidence of inflammatory myocarditis. Although there have been reports of peripheral eosinophilia associated with multiple drugs of abuse, the patient denied any recent exposure to them, and urine and serum toxicology screens were also negative. There were no signs or symptoms of intoxication or withdrawal throughout her hospitalization to suggest illegal drug-induced eosinophilia. Although cardiac involvement can be associated with antineutrophil cytoplasmic antibody-negative CSS, our patient did not demonstrate upper respiratory manifestations and did not respond to corticosteroids, which are characteristic features of CSS. In addition, presence of mild dyspoietic changes in the myeloid elements are features that support a primary hematologic disorder rather than an autoimmune disease.

Cardiac involvement has been reported on numerous occasions in HES, particularly Loeffler endomyocarditis, and is more common in M-HES. The most commonly reported molecular aberration in M-HES is a fusion of uncharacterized Fip1-like 1 (FIPL1) and platelet-derived growth factor receptor-α (PDGFRA) genes, producing activation of PDGFRA. In these patients, other phenotypic aberrations, including increased serum tryptase, atypical mast cells, and tissue fibrosis, can be seen. The presence of the rearrangement is important, as individuals can be treated with imatinib mesylate (Gleevec). In this case, the FIPL1–PDGFRA fusion was not identified by fluorescence in situ hybridization.

Although definitive diagnosis of HES requires persistent eosinophilia of more than 6 months’ duration, our patient’s end organ damage secondary to eosinophilia, namely asthma and myocarditis, are highly suggestive of HES. Although WS is by definition limited to a recurrent granulomatous and eosinophilic dermatosis, few isolated cases of WS with multiorgan involvement mimicking HES have been reported, suggesting a continuum between these entities (Table 1). We propose that the diagnoses of WS and HES are not mutually exclusive; rather, they represent a spectrum of eosinophilic disease. The degree of peripheral eosinophilia and the degree of degranulation of eosinophils in cutaneous tissue tend to lead clinicians toward a diagnosis of WS and HES, respectively; however, it is clear that there is considerable overlap between the 2 entities. Although flame figures are not considered typical of HES skin lesions, neither are they pathognomonic for WS. Perhaps WS represents a more severe form of the cutaneous manifestations of HES.

Finally, we would like to point out that in all the cases of potential overlap between WS and HES, resolution of the cutaneous manifestations resulted following courses of systemic corticosteroids. However, although most patients respond to high-dose corticosteroids, hydroxyurea has been reported as a successful second-line agent for resistant cases of HES. In our patient, initiation of hydroxyurea therapy induced complete resolution of both her systemic and cutaneous symptoms. Thus, if we regard WS and HES as a spectrum, it is reasonable to extrapolate that physicians should
## TABLE 1. WS and HES Cases. Case Reports of Concomitant Features of WS and HES

| Patient         | Age (Yr) and Sex | Duration of Eosinophilia | Cutaneous Findings                                                                 | Extracutaneous Manifestations                                                                 | Histopathologic Findings                                                                 | Treatment and Outcome                                                                 |
|-----------------|------------------|--------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Bogentieder et al\(^{14}\) | 38 F             | ≥2 wk with multiple episodes | Pruritic, erythematous, edematous and occasional vesicular lesions on trunk, lower legs | Myalgias, arthralgias, headaches, fatigue, blurred vision, sensory disturbances, dyspnea, asthma, bronchoalveolar lavage-proven bronchial eosinophilia, eosinophilic myocarditis | Dermal infiltration by eosinophils and flame figures | 0.1% triamcinolone-hydrochloride lotion, IV prednisone with oral taper with complete resolution. Recurrence 22 months later resolved with oral prednisone |
| Carlesimo et al\(^{7}\) | 69 M             | ≥1 mo                    | Pruritic, erythematous, edematous plaques and papulovesicular lesions on trunk, extremities | Submandibular lymphadenopathy, parotid gland enlargement, fever, fatigue, pancreas enlargement, pulmonary embolism | Diffuse dermal infiltration by eosinophils; no flame figures appreciated | IV betamethasone with oral methylprednisolone taper and heparin with complete resolution |
| Fujii et al\(^{9}\) | 60 M             | ≥12 mo                   | Pruritic, erythematous urticarial and tender, erythematous plaques on trunk          | Obstructive lung disease with productive cough, epigastric pain, axonal peripheral neuropathy | Dermal infiltration by eosinophils and flame figures | Systemic prednisolone with resolution of erythematous plaques, epigastric pain, and peripheral neuropathy; no resolution of eosinophilia, urticaria or bronchospasm |
| Fujii et al\(^{8}\) | 35 F             | ≥15 yr                   | Tender, erythematous plaque and erythematous urticaria on trunk                    | Obstructive lung disease, epigastric cramping with proven eosinophilia of the lamina propria on gastric mucosal biopsy | Papillary dermal edema and perivascular infiltration of eosinophils; no flame figures appreciated | Systemic prednisolone with resolution; however, tapering steroids persistently results in relapse of all symptoms and eosinophilia |
| Fujii et al\(^{8}\) | 26 M             | ≥10 mo                   | Pruritic, indurated erythema and erythematous urticaria on left pretibial area      | Severe abdominal pain with biopsy-proven necrosis, mucosal microthrombi and transmural infiltration of monocytes and eosinophils | Mid to reticular dermal infiltration by eosinophils, papillary dermal perivascular eosinophilic infiltration, and flame figures | Systemic betamethasone with presumed resolution, followed by representation and spontaneous resolution after 10 mo |
| Tsuji et al\(^{15}\) | 42 F             | Unknown                  | Pruritic, edematous erythema on the lower legs and hard subcutaneous nodules in the groin | Pulmonary eosinophilia and productive cough with lung biopsy-proven alveolar and interstitial eosinophilic infiltrate, asthma, bronchoectasia, and biopsy-proven eosinophilic infiltration of the inguinal lymph nodes | Dermal infiltration by eosinophils and flame figures | Topical corticosteroids initially with gradual resolution of the skin lesions; with relapse, treated with oral prednisolone with resolution of skin lesions and pulmonary manifestations. The subcutaneous nodules in the groin persisted |

Consider usage of hydroxyurea in patients with WS who are refractory to treatment with systemic corticosteroids.

WS and HES are 2 well-described entities in the literature; however, we suspect that their concomitant presence is underreported, and that these 2 diseases may represent distinct points on a spectrum of hypereosinophilic disease. Although a diagnosis of WS should be reserved for patients without systemic manifestations, its clinical and histologic diagnosis...
should always prompt a careful work-up to exclude the possibility of a more aggressive hematologic disorder. Further investigation of the cutaneous and histopathologic findings of patients meeting the criteria for HES should be pursued.

IV, intravenous, F, female; M, male.

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