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

Sabrina M. Smith, BA, Elizabeth A. Kiracofe, MD,* Lindsey N. Clark, MD,† and Alejandro A. Gru, MD*†*

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

(*Am J Dermatopathol* 2015;37:910–914)

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 arthalgias.[1] Conversely, in HES, most patients also present with peripheral eosinophilia and systemic involvementand 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 $\times$ $10^3/\mu L$, normal (nml): 4.5–11 $\times$ $10^3/\mu L$] 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*, *FIPL1–PDGFRA,* 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/antineutrophilic cytoplasmic antibody, and infections

From the Departments of *Dermatology, and †Pathology, Wexner Medical Center, The Ohio State University, Columbus, OH.

Supported by the Department of Dermatology, Wexner Medical Center, The Ohio State University.

The authors declare no conflicts of interest.

E. A. Kiracofe and A. A. Gru had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* S. M. Smith, E. A. Kiracofe, L. N. Clark, and A. A. Gru. *Acquisition, analysis, and interpretation of data:* S. M. Smith, E. A. Kiracofe, L. N. Clark, and A. A. Gru. *Drafting of the manuscript:* S. M. Smith. *Critical revision of the manuscript for important intellectual content:* E. A. Kiracofe. *Study supervision:* A. A. Gru.

Reprints: Sabrina M. Smith, BA, Department of Dermatology, Wexner Medical Center, The Ohio State University, 4181 Graves Hall, 333 W 10th Avenue, Columbus, OH 43210 (e-mail: sabrina.smith@osumc.edu).

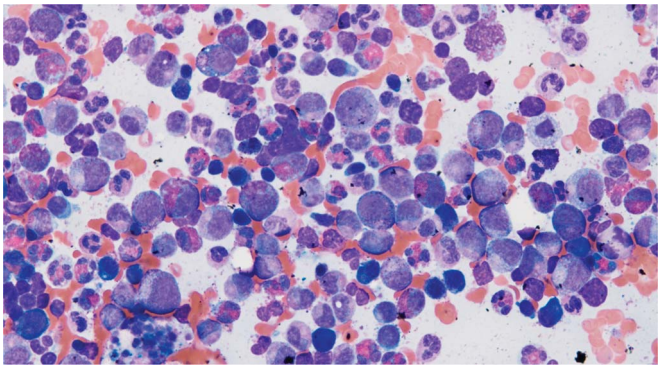

FIGURE 1. Numerous eosinophils with dysplastic features including hypo- and hypersegmented nuclei with abnormal distribution of granules (Wright–Giemsa, magnification ×600).

(including parasites) were all negative. During hospitalization, the patient developed scattered erythematous, irregularly shaped, mildly indurated, tender papules on her lower back and abdomen (Fig. 2). She was also found to have bilateral palmar erythema with prominent clearing of the thenar and hypothenar eminences as well as fine telangiectasias over the chest and neck. Clinically, the differential diagnosis included leukemia cutis in the setting of possible HES and a punch biopsy was performed. Histologically, a diffuse eosinophilic infiltrate extending from the papillary dermis into the subcutis was present (Figs. 3–5). Collagen degeneration with deposition of eosinophilic major basic protein forming "flame figures" were readily identified (Fig. 6), all features reminiscent of eosinophilic cellulitis (WS).

Since the patient's eosinophilia was refractory to conventional high-dose steroids, she was started on hydroxurea 500 mg daily. One week after discharge, her leukocytosis had resolved ($6.1 \times 10^3/\mu L$, nml: $4.5–11 \times 10^3/\mu L$), with moderate improvement in her eosinophilia (28%, nml: 0%–5%). Forty days after presentation, her eosinophilia had resolved. Monitoring at 6 months revealed that the patient has continued to show improvement, with complete resolution of her leukocytosis, eosinophilia, myocarditis, and cutaneous lesions.

DISCUSSION

WS, or eosinophilic cellulitis, was first described in 1971 by Wells[3] 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[4] recently

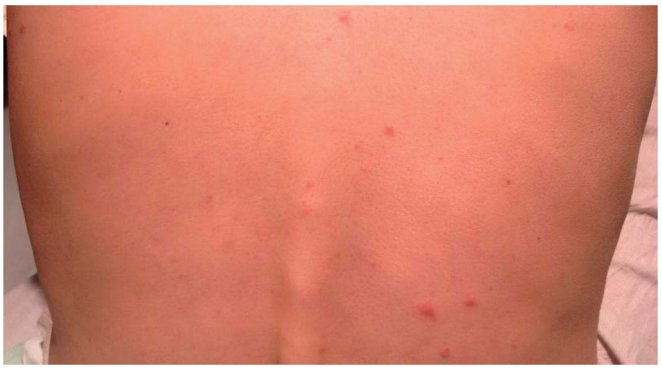

FIGURE 2. Patient's trunk, demonstrating erythematous, irregular papular rash of WS.

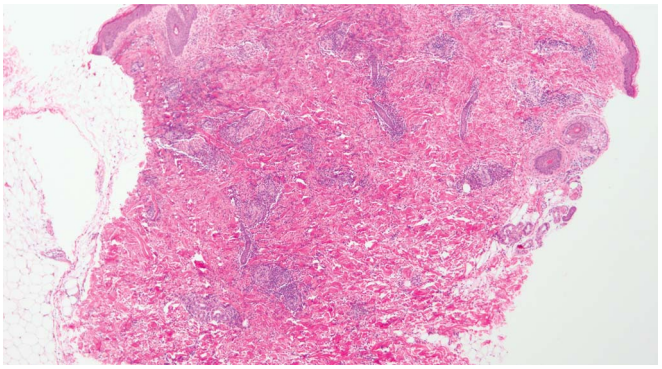

FIGURE 3. Skin biopsy showing a diffuse dermal infiltrate extending from the superficial papillary dermis into the deep reticular dermis (hematoxylin and eosin, magnification, ×20).

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.[4]

Three histopathologic stages of WS have been described.[5] 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.[1] The resolution stage shows palisading histiocytes surrounding the flame figures with occasional necrobiosis. Flame figures are suggestive, although not pathognomonic, of WS. In 1 review, flame figures were observed in 96% of cases diagnosed as WS.[1] 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).[1,5]

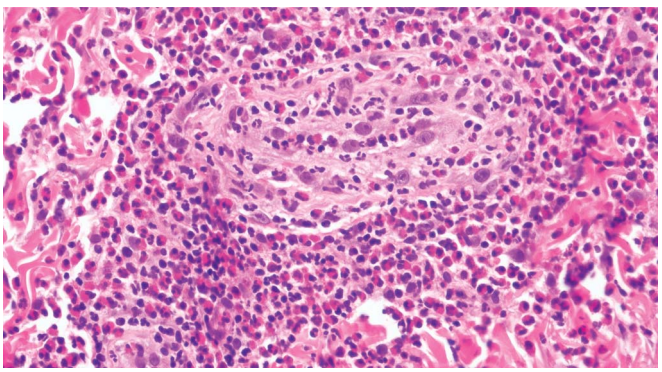

FIGURE 4. Marked interstitial dermal eosinophilia with infiltration into piloerector muscles (hematoxylin and eosin, magnification, ×200).

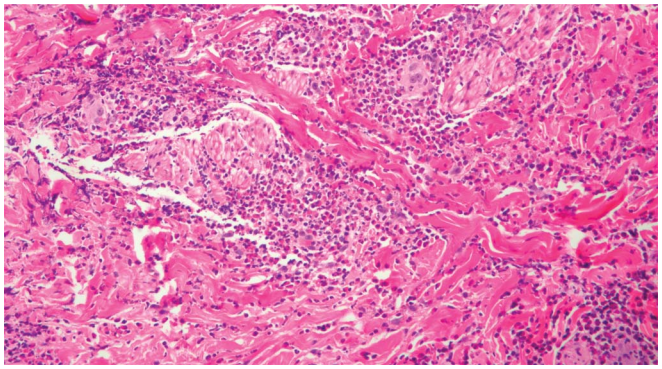

FIGURE 5. Extensive peri- and intravascular eosinophilia without diagnostic evidence of a vasculitis (hematoxylin and eosin, magnification, ×400).

The diagnostic criteria for idiopathic HES were first outlined in 1975 by Chusid et al.[6] 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.[7] 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.[2] Flame figures have been only rarely associated with HES; this is thought to be the result of insufficient eosinophil degranulation.[8,9] Interestingly, both WS and HES have been associated with increased expression of CD25 on the surface of eosinophils[10] and the presence of eosinophil extracellular DNA traps.[11] 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.[10,11]

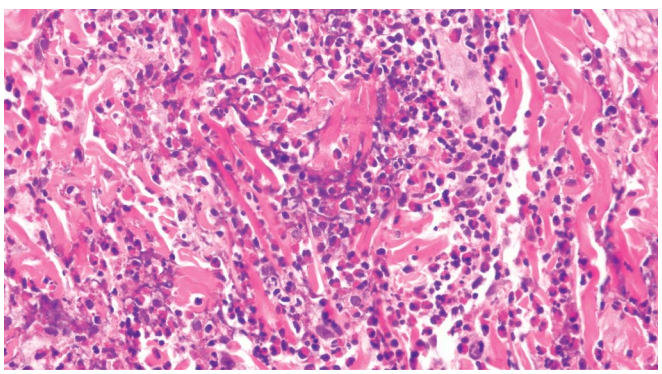

FIGURE 6. A dense eosinophilic infiltrate with degranulation of many eosinophils with subsequent formation of conspicuous flame figures is seen throughout the dermis. (hematoxylin and eosin, magnification, ×200).

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,[12] 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 antineutrophilic cytoplasmic antibody-negative CSS,[13] 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.[7] 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).[7] In this case, the *FIP1L1–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.[7] 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
Bogenrieder 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[8]	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[9]	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[9]	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.

REFERENCES

1. Sinno H, Lacroix JP, Lee J, et al. Diagnosis and management of eosinophilic cellulitis (Wells' syndrome): a case series and literature review. *Can J Plast Surg.* 2012;20:91–97.
2. Kazmierowski JA, Chusid MJ, Parrillo JE, et al. Dermatologic manifestations of the hypereosinophilic syndrome. *Arch Dermatol.* 1978;114:531–535.
3. Wells GC. Recurrent granulomatous dermatitis with eosinophilia. *Trans St Johns Hosp Dermatol Soc.* 1971;57:46–56.
4. Caputo R, Marzano AV, Vezzoli P, et al. Wells' syndrome in adults and children: a report of 19 cases. *Arch Dermatol.* 2006;142:1157–1161.
5. Weiss G, Shemer A, Confino Y, et al. Wells' syndrome: report of a case and review of the literature. *Int J Dermatol.* 2001;40:148–152.
6. Chusid MJ, Dale DC, West BC, et al. The hypereosinophilic syndrome: analysis of fourteen cases with review of the literature. *Medicine (Baltimore).* 1975;54:1–27.
7. Plotz SG, Huttig B, Aigner B, et al. Clinical overview of cutaneous features in hypereosinophilic syndrome. *Curr Allergy Asthma Rep.* 2012;12:85–98.
8. Carlesimo M, Fidanza L, Mari E, et al. Wells syndrome with multiorgan involvement mimicking hypereosinophilic syndrome. *Case Rep Dermatol.* 2009;1:44–48.
9. Fujii K, Tanabe H, Kanno Y, et al. Eosinophilic cellulitis as a cutaneous manifestation of idiopathic hypereosinophilic syndrome. *J Am Acad Dermatol.* 2003;49:1174–1177.
10. Simon HU, Plotz S, Simon D, et al. Interleukin-2 primes eosinophil degranulation in hypereosinophilia and Wells' syndrome. *Eur J Immunol.* 2003;33:834–839.
11. Simon D, Hoesli S, Roth N, et al. Eosinophil extracellular DNA traps in skin diseases. *J Allergy Clin Immunol.* 2011;127:194–199.
12. Mayron LW, Alling S, Kaplan E. Eosinophilia and drug abuse. *Ann Allerg.* 1972;30:632–637.
13. Bouiller K, Samson M, Eicher JC, et al. Severe cardiomyopathy revealing antineutrophilic cytoplasmic antibodies-negative eosinophilic granulomatosis with polyangiitis. *Intern Med J.* 2014;44:928–931.
14. Bogenrieder T, Griese DP, Schiffner R, et al. Wells' syndrome associated with idiopathic hypereosinophilic syndrome. *Br J Dermatol.* 1997;137:978–982.
15. Tsuji Y, Kawashima T, Yokota K, et al. Wells' syndrome as a manifestation of hypereosinophilic syndrome. *Br J Dermatol.* 2002;147:811–812.