

Dermatologic Manifestations of the Hypereosinophilic Syndromes

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Hypereosinophilic syndromes (HES) may present with cutaneous abnormalities (Box 1). Over 50% of patients have pruritic erythematous macules, papules, plaques, wheals, nodules, or other skin lesions during the course of the disease [1,2], but a diagnosis of HES may be delayed or missed because association between such lesions and HES is not appreciated. Urticaria and angioedema occur in all HES subtypes and are characteristic of certain variant subtypes. Eosinophil granule proteins are deposited diffusely in skin lesions of HES and may mediate increased vasopermeability, resulting in edema and other effects. In addition, there are a variety of cutaneous reaction patterns to consider in evaluating diseases characterized by eosinophilia of peripheral blood and/or tissues (Box 2). The skin diseases discussed in this article are presented based on the classification of HES put forth in the publication resulting from the 2005 workshop summary of the International Eosinophil Society meeting [3].

Sections of this article have been modified from the following documents: Leiferman KM, Peters MS. Eosinophils in cutaneous diseases. In: Wolff K, Goldsmith LA, Katz SI, et al, editors. Fitzpatrick's Dermatology in General Medicine. 7th edition. New York: McGraw-Hill, Inc., in press; and Stetson CL, Leiferman KM. Eosinophilic Dermatoses. In: Bologna JL, Jorizzo JL, Rapini RP, et al, editors. Dermatology. 2nd edition. St. Louis: Mosby, in press.

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Box 1. Hypereosinophilic syndromes: mucocutaneous signs, symptoms, and diagnoses

Angioedema
Eczema
Erosions
Erythema
Erythema annulare centrifugum
Erythroderma
Excoriations
Livedo reticularis
Macules
Mucosal (oral and genital) ulcers
Nail fold infarcts
Necrotizing vasculitis
Nodules
Papules
Patches
Pruritus
Purpuric papules
Splinter hemorrhages
Ulcers
Urticaria
Vasculitis
Wells' syndrome (eosinophilic cellulitis)

Eosinophils and the skin*Normal skin*

The presence of eosinophils in normal tissues is surprisingly selective. Eosinophils infiltrate the spleen, lymph node, and thymus, with scant evidence of granule protein deposition. The only organ other than the bone marrow that normally shows both eosinophil infiltration and remarkable degranulation is the gastrointestinal tract [4]. Eosinophil infiltration or degranulation is not seen in skin from normal persons or from normal skin of patients with a variety of disorders [4–6].

Eosinophil infiltration

Mechanisms of eosinophil infiltration in tissues, including skin, have been studied extensively, as reviewed by Bochner and Ackerman elsewhere in this issue. Eosinophils are attracted into tissues and activated by at least three interrelated signals: (1) chemoattractants, (2) adhesion molecules, and (3)

Box 2. Deposition of eosinophil granule proteins in cutaneous diseases

Edema

Chronic urticaria

Solar urticaria

Delayed pressure urticaria

IgE-mediated late phase reaction

Episodic angioedema with eosinophilia (Gleich's syndrome)

Facial edema with eosinophilia

Nodules, eosinophilia, rheumatism, dermatitis,
swelling syndrome

Granulocyte macrophage colony-stimulating factor reaction

Interleukin-2 capillary leak syndrome

Eczematoid reactions

Atopic dermatitis

Onchocercal dermatitis

Prurigo nodularis

Pachydermatous eosinophilic dermatitis

Vasculitis

Churg-Strauss syndrome

Recurrent cutaneous eosinophilic vasculitis

Eosinophilic vasculitis in connective tissue disease

Blisters

Bullous pemphigoid

Pemphigoid (herpes) gestationis

Bullous morphea

Blisters in Churg-Strauss syndrome

Incontinentia pigmenti

Fibrosis

Eosinophilia myalgia syndrome

Toxic oil syndrome

Eosinophilic fasciitis

Data from Leiferman KM, Peters MS. Eosinophils in cutaneous diseases. In: Wolff K, Goldsmith LA, Katz SI, et al, editors. Fitzpatrick's Dermatology in General Medicine. 7th edition. New York: McGraw-Hill, Inc., in press.

activating cytokines [7,8]. Eotaxins 1–3 and “regulated on activation normal T cell–expressed and secreted” (RANTES) are produced by dermal fibroblasts, and RANTES also is produced by keratinocytes. Eosinophil-selective adhesion molecule expression and other eosinophil-activating cytokines also

may be induced in skin. Thus, eosinophil signaling is poised for participation in cutaneous inflammation [9,10].

Eosinophil degranulation

As intact cells, eosinophils are readily identified by their tinctorial properties when stained with the acidic dye, eosin. Cytoplasmic granules in eosinophils are distinctive both in composition (namely, cationic proteins that are responsible for their cellular staining properties) and ultrastructural features identified by electron microscopy. Like other granulated cells, eosinophils undergo degranulation. Degranulation refers to the release of eosinophil granule proteins and is defined herein as extracellular deposition of eosinophil granule major basic protein (MBP) or other distinctive granule proteins, which can be detected in tissues by special stains.

Eosinophil degranulation can occur through classical exocytosis or piecemeal degranulation, but, in skin diseases, commonly occurs by cytolysis in skin diseases. A study of lesional skin from patients with atopic dermatitis showed intact eosinophils with abnormal granules and with disrupted cytoplasmic and/or nuclear membranes; membrane-bound granules were present in the dermis near to and in the absence of degenerating eosinophils [11]. There was no evidence of classical granule exocytosis. Disrupted eosinophils have been observed in the dermis of lesional tissue from patients with episodic angioedema associated with eosinophilia [12] and the IgE-mediated late phase reaction [13]. Therefore, deposition of eosinophil granule proteins in skin occurs after eosinophil cytolysis. A similar conclusion was reached through study of involved skin from a patient with HES [14].

Eosinophils and cutaneous edema

Eosinophils may induce cutaneous edema [7] through direct effects on blood vessels or indirectly through mast cells. Topical administration of nanomolar concentrations of eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), and MBP increases vasopermeability in the hamster cheek pouch [15,16]; neither histamine nor nitric oxide appears to participate in this effect [15,17]. Injection of approximately 5 $\mu\text{mol/L}$ of MBP into guinea pig skin increases cutaneous vasopermeability [18]. Intradermal injection of eosinophil granule proteins elicits a wheal-and-flare reaction in human skin [12,19]. In vitro, micromolar concentrations of MBP and ECP inconsistently induce histamine release from mast cells and basophils [20,21]. Stem cell factor is required for MBP to induce histamine release from certain types of human mast cells [22].

The lowest detectable concentrations of eosinophil granule proteins in the skin are 0.05 $\mu\text{mol/L}$ EPO, 0.1 $\mu\text{mol/L}$ MBP, 0.25 $\mu\text{mol/L}$ ECP, and 1 $\mu\text{mol/L}$ eosinophil-derived neurotoxin (EDN) [23]. After injection into guinea pig skin, these proteins persist in vivo for 1 (EPO), 2 (ECP), 2½ (EDN), or

6 (MBP) weeks [23]. Each protein increases cutaneous vasopermeability in a concentration-dependent fashion, with potencies comparable to that of histamine [23]. Pretreatment of guinea pigs with an antihistamine, pyrilamine maleate, does not inhibit the increased vasopermeability induced by ECP and EDN but significantly inhibits that induced by EPO and MBP [23]. Micromolar concentrations of eosinophil granule proteins are commonly deposited in the skin of eosinophil-associated cutaneous disorders (see Box 2), such as atopic dermatitis, and probably increase cutaneous vasopermeability (by histamine-independent and -dependent mechanisms), potentially altering cutaneous function for days to weeks.

Of the skin disorders characterized by swelling [24], eosinophil involvement has been particularly well demonstrated in chronic urticaria [6], pressure urticaria [25], and episodic angioedema (see Box 2) [12]. In addition to intact eosinophils, lesions of urticaria contain prominent extracellular deposition of granule proteins around small blood vessels, dispersed in the dermis, and on connective tissue fibers, in up to 60% of cases [6]. Sequential biopsy specimens from lesions of solar and delayed pressure urticaria, and from lesions elicited by a solar simulator or dermographometer [25,26], demonstrate a pattern of eosinophil and neutrophil degranulation similar to that seen in the IgE-mediated late phase reaction [13], which exhibits erythema, edema, pruritus, warmth, and tenderness. Skin biopsy specimens from patients with episodic angioedema associated with eosinophilia and its localized variant, recurrent facial edema with eosinophilia [12,27], show few eosinophils, but immunofluorescence staining reveals extracellular deposition of eosinophil granule proteins around blood vessels and on collagen bundles [12]. Capillary leak syndromes due to administration of interleukin (IL)-2 and granulocyte macrophage colony-stimulating factor are associated with peripheral blood eosinophilia, increased serum IL-5 levels, and eosinophil degranulation [28,29]. The ability of eosinophils to elaborate vasoactive mediators that elicit cutaneous wheal-and-flare reactions, along with the presence of granule proteins in edematous skin, support a role for eosinophils as key participants in the edema associated with certain cutaneous diseases.

Cutaneous aspects of hypereosinophilic syndrome

Patients who fulfill diagnostic criteria for HES (as reviewed by Sheikh and Weller elsewhere in this issue) develop symptoms related to the organ systems infiltrated by eosinophils. Occurring in over 50% of HES patients, skin lesions, of the trunk and/or extremities, may be the first manifestation of HES [2], and include pruritic erythematous macules, papules, plaques, wheals, and nodules [1]. Urticaria and angioedema occur in all HES subtypes and are characteristic of certain subtypes. HES patients may present with or develop a variety of cutaneous disorders, including erythema

annulare centrifugum [30–32], necrotizing vasculitis [33,34], livedo reticularis, purpuric papules [33], and Wells' syndrome (eosinophilic cellulitis) [35,36].

Myeloproliferative hypereosinophilic syndrome variant

The presenting complex of myeloproliferative HES (reviewed by Bain and Fletcher elsewhere in this issue) often includes skin lesions in addition to fever, weight loss, fatigue, malaise, and hepatosplenomegaly [37]. Splinter hemorrhages and/or nail fold infarcts may herald the onset of thromboembolic disease associated with eosinophilic endomyocardial involvement, and this constitutes a medical emergency because of potentially serious sequelae. A distinctive feature of patients with myeloproliferative HES is mucosal ulceration [38,39]. The initial report of this association described two patients who satisfied diagnostic criteria for HES: both had eosinophil counts greater than $1500/\text{mm}^3$ for more than 6 months; organ–system involvement, including heart and skin; and no evidence of parasitic, allergic, or other known causes of eosinophilia. In both patients, an initial diagnosis of Behcet's syndrome was based on severe, chronic, and recurrent oral and genital ulcers, but all other major criteria (uveitis, synovitis, cutaneous vasculitis, and meningoencephalitis) for Behcet's syndrome were absent. Furthermore, mucosal ulcers in these patients (Fig. 1) often exceeded the size (1 cm diameter) typically associated with aphthae of Behcet's disease. Both patients died, as did 4 of 7 additional patients. The prognosis of this HES variant remained relatively poor until mucosal ulcers in several patients showed dramatic response to administration of a tyrosine kinase inhibitor, imatinib mesylate (Gleevec) [40]. Furthermore, responsiveness to imatinib is associated with a mutational deletion on chromosome 4, resulting in a fusion gene, Fip1-like-1/platelet-derived growth factor receptor α (FIP1L1-PDGFR α), and generation of an imatinib-sensitive kinase [41,42]. Recently, Klion and colleagues [43] found serum tryptase levels (marking mast cell activity) greater than 12 ng/mL in 9 of 15 patients with HES; 3 of the 9 had mucosal ulcers

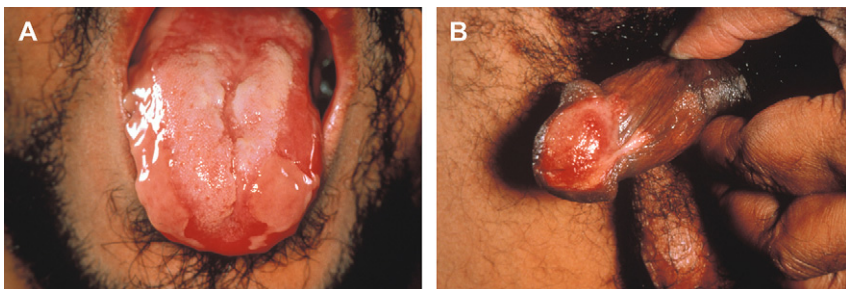


Fig. 1. Mucosal erosions and ulcers of the tongue (A) and glans penis (B) in a patient who has myeloproliferative HES.

and were categorized as having myeloproliferative HES with tissue fibrosis. Overall, these findings suggest that patients with mucosal ulceration and HES are distinctive both in cutaneous manifestations and biologic behavior of their disease. Testing for FIP1L1-PDGFR α should be performed in HES patients because of the striking therapeutic effectiveness of imatinib.

Lymphocytic hypereosinophilic syndrome variant

Lymphocytic HES (reviewed by Roufosse, Cogan, and Goldman elsewhere in this issue) is associated with severe pruritus, eczema, erythroderma, urticaria, and angioedema, as well as lymphadenopathy, and endomyocardial involvement, although cardiac abnormalities occur less commonly than in myeloproliferative HES. Many of these patients have T cell clones that produce IL-5 [44,45]. In contrast to myeloproliferative HES, lymphocytic HES generally follows a benign course, and T cell clones can remain stable for years. Patients should be regarded as having premalignant or malignant T cell proliferation [45], because the disease may evolve into lymphoma. In 3 patients who had lymphocytic HES, repeated infusion of an antibody to IL-5, mepolizumab, effectively controlled their eosinophilic dermatitis [46]; after the first infusion, pruritus decreased and pruritic, eczematous, and urticarial skin lesions regressed; within 24 hours, eosinophil counts dropped to normal, and serum ECP levels became normal during the next 2 days. There was no systemic or local toxicity, including leukopenia or changes in the distribution of lymphocyte subpopulations, indicating that mepolizumab does not cause general immunosuppression. In 2 of 3 patients, mepolizumab was associated with decreased in vitro T helper 2 cytokine production following mitogen stimulation of T cells. These data suggest that eosinophils are able to modulate T cell function, including differentiation and cytokine production, and that treatment of lymphocytic HES with anti-IL-5 should be effective.

Undefined hypereosinophilic syndrome: episodic angioedema associated with eosinophilia

Classified as “undefined” [3], this distinct HES subset is characterized by severe, cyclical attacks of angioedema (Fig. 2) that involve the face, neck, trunk and extremities, urticaria, fever, marked peripheral blood eosinophilia (up to 100,000 cells/ μ L), and an average increase in body weight of 14% (range, 10%–18%) [12]. Attacks persist for days. Marked leukocytosis and eosinophilia appear to vary in parallel with the clinical severity of the attack. In addition, there is a polyclonal increase in serum IgM levels, and IgE levels may be strikingly high. The disease occurs in children and adults [47,48], and localized variants are described [27].

Serum IL-5 levels are increased in episodic angioedema. During prednisone treatment (administered daily, every other day, or in short [3- to 5-day] courses [7]), IL-5 becomes undetectable as patients improve clinically,



Fig. 2. Episodic angioedema with eosinophilia in a 2-year-old girl with marked edema of the face during an attack (A) compared with normal appearance between episodes (B). (From Katzen DR, Leiferman KM, Weller PF, et al. Hypereosinophilia and recurrent angioneurotic edema in a 2 1/2-year-old girl. *Am J Dis Child* 1986;140:63; with permission.)

lose weight, and eosinophil counts decrease [49]. In one patient studied over a 3-week period, maximum IL-5 levels and minimum urine output occurred on days 13 and 14; maximum eosinophil counts occurred on days 16 and 17, and peak weight was reached on day 18 [49]. Interestingly, peak eosinophilia lagged behind the peak serum IL-5 level by approximately 3 to 4 days [49]; this may represent the time needed for late stage eosinophil progenitors to fully differentiate into mature eosinophils and gain access to the peripheral blood. IL-5 levels spontaneously decreased during the latter stages of the attacks (Fig. 3). In this patient, intravascular fluid overload developed following prednisone administration, with resultant bradycardia, orthopnea, and bibasilar pulmonary infiltrate, without evidence of cardiac dysfunction. In addition, an increased percentage of activated T helper cells preceded the development of elevated IL-5 levels. A previously reported patient with episodic angioedema and eosinophilia had normal percentages of peripheral blood CD4 helper cells and CD8-positive cells; however, 32% of the CD4 cells expressed the HLA-DR activation antigen (normal value, <2%) [48]. The patient discussed here had a similar percentage (28%) of CD3-positive T cells expressing the HLA-DR activation antigen 10 days before the maximal eosinophil count [49]. Additional markers of T cell activation found in patients with episodic angioedema include IL-1 and soluble IL-2 receptor [50], and patients with this syndrome have developed T cell clones [51,52]. Peripheral blood eosinophils may lack CD69 expression, in contrast to the immunophenotype in other forms of HES [53].

In summary, very high levels of IL-5 are produced in episodic angioedema associated with eosinophilia. IL-5 stimulates bone marrow and activates eosinophils; eosinophils migrate into skin and deposit their granule proteins. These proteins, leukotrienes, and arachidonic acid metabolites contribute to massive increases in vascular permeability. As the stimuli for

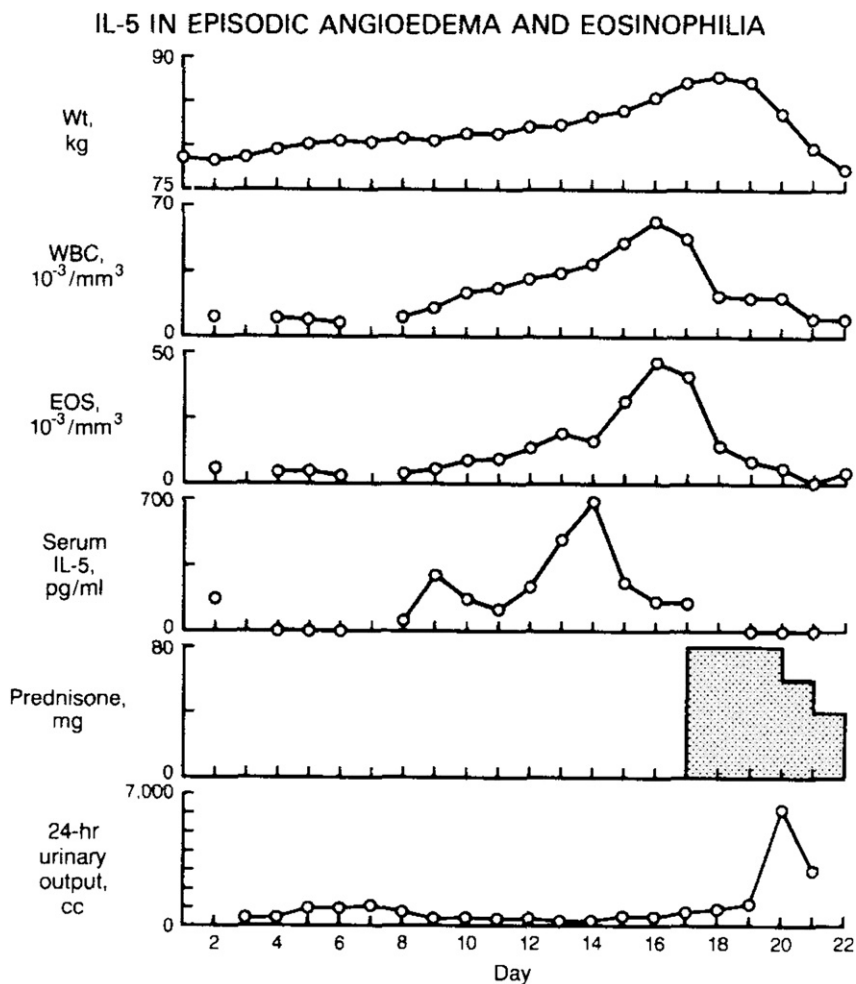


Fig. 3. Episodic angioedema with eosinophilia: clinical and laboratory findings include a bi-phasic increase in IL-5 levels during an attack, which by day 16 (the day of maximal eosinophilia) was decreasing. Prednisone administration was associated with disappearance of detectable IL-5 in serum. (From Butterfield JH, Leiferman KM, Abrams J, et al. Elevated serum levels of interleukin-5 in patients with the syndrome of episodic angioedema and eosinophilia. *Blood* 1992;79:689; with permission.)

eosinophil production diminish, the clinical abnormalities remit. However, the mechanisms causing the periodic elevations of IL-5 with corresponding eosinophilia are still obscure.

Nodules, eosinophilia, rheumatism, dermatitis, and swelling syndrome

Associated with marked peripheral blood eosinophilia and episodic swelling of the hands and feet, this syndrome was reported initially in 2 patients

who also had dermatitis, nontender compressible articular nodules arising from the tenosynovium of extensor tendons, and pain in adjacent muscles and joints [54]. One of the two originally reported patients had dermographism as well as episcleritis. Both patients had increased plasma levels of MBP and EDN and increased serum IgE and IgM levels. Histologic evaluation of nodules revealed tenosynovitis with necrotizing granulomas, nonspecific vasculitis, eosinophil infiltration, and numerous mast cells; immunostaining for MBP provided evidence of degranulation. Lesions responded to low doses of prednisone. One patient had eosinophilia greater than 1500/mL blood for over 15 years without developing cardiovascular disease [54]. Patients with nodules, eosinophilia, rheumatism, dermatitis, and swelling syndrome have activated T cells [55] and also have developed T cell clones [52].

Associated hypereosinophilic syndrome: Churg–Strauss syndrome

Churg–Strauss syndrome (CSS) satisfies the criteria for HES and is classified as “associated HES” [3] because it is a recognized syndrome. Also termed allergic granulomatosis, CSS was described in 1951 as a complex of systemic vasculitis, asthma, and eosinophilia [56]. Cutaneous lesions are characterized by eosinophil infiltration, necrotizing vasculitis, and extravascular granulomas. Eosinophil mediators are prominent in lesions (Fig. 4) [57]. CSS affects respiratory tissues with asthma and sinus disease and is associated with involvement of other organs [58], including the heart and particularly the skin. Patients have cutaneous papules and nodules of the scalp or extremities and hemorrhagic lesions ranging from petechiae to blisters and eschars (Fig. 5). CSS is discussed by Wechsler elsewhere in this issue.

Overlap hypereosinophilic syndrome: eosinophilia myalgia syndrome and the Spanish toxic oil syndrome

Eosinophilia myalgia syndrome (EMS) and toxic oil syndrome (TOS) share many features, particularly cutaneous manifestations. EMS first presented in the fall of 1989 as a novel disease in epidemic form [59]. Although it is not known how long the syndrome had been in existence, a patient with EMS who was first seen in 1986 subsequently confirmed daily use of L-tryptophan for 5 years before onset of symptoms. Essentially all patients had severe myalgias early in the disease [59,60]. In addition to the characteristic features of eosinophilia and disabling myalgias, patients typically suffered multiorgan dysfunction, including fasciitis, pneumonitis, pulmonary hypertension, myocarditis, peripheral neuropathy, encephalopathy, cystitis, and peribiliary inflammatory fibrosis. In some fatal cases, peripheral neuropathy resulted in respiratory paralysis and death. Cutaneous abnormalities consisted of edema, pruritus, faint confluent erythema, hair loss, peau d’orange, and morphea-like skin lesions [61].

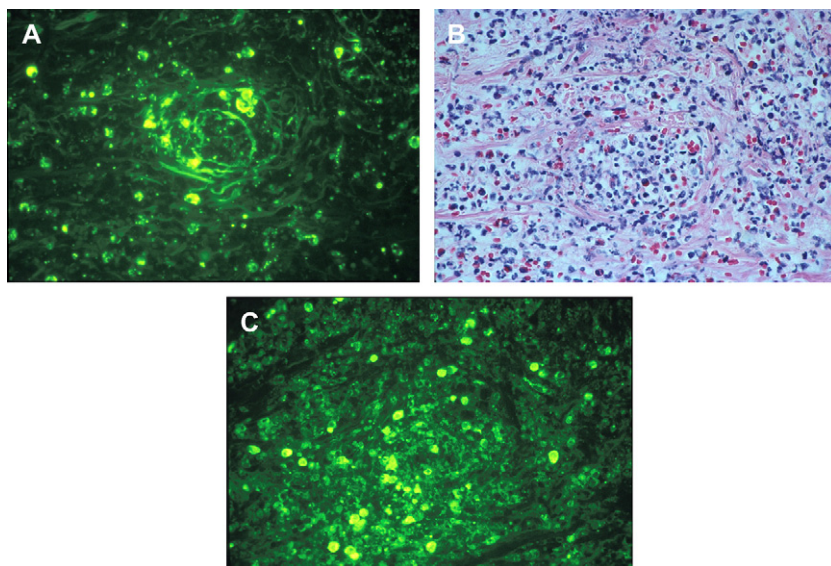


Fig. 4. Cutaneous leukocytoclastic vasculitis in Churg-Strauss syndrome: heavy mixed inflammatory cell infiltrate with numerous eosinophils and eosinophil granule products. MBP in and around a damaged blood vessel (*A*) (original magnification $\times 400$) as demonstrated in the same section counterstained by hematoxylin and eosin (*B*) (original magnification $\times 400$). A serial section (*C*) is stained for EDN and reveals prominent cellular and extracellular EDN in and around the damaged blood vessel (original magnification $\times 400$).

The pathologic hallmarks of EMS are inflammation involving fibrous connective tissue and occlusive microangiopathy. The inflammatory infiltrate consists of mononuclear cells and few to many eosinophils. There is marked deposition of eosinophil granule proteins, often exceeding the degree of infiltration by intact eosinophils [59,62]. The severe myalgias at rest may be related to inflammation of fascial and intramuscular nerves;

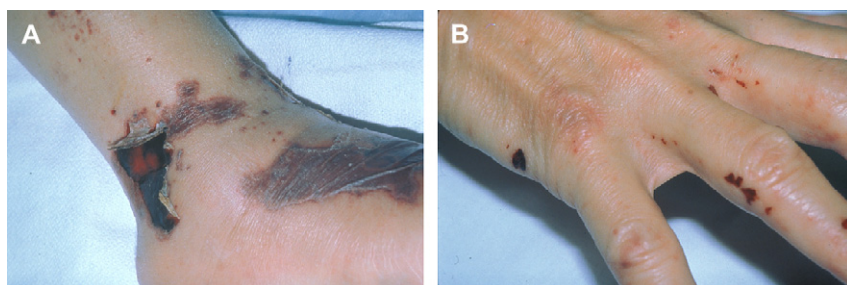


Fig. 5. Skin lesions in Churg-Strauss syndrome. (*A*) Characteristic hemorrhagic bullae and palpable purpura involving the foot. (*B*) Hemorrhagic infarcted lesions of the hand.

irritation or injury of peripheral nerves by EDN, other toxic eosinophil granule proteins and/or eosinophil products such as superoxide ion; or ischemia of nerves caused by occlusive microangiopathy [62]. Ischemia also may be responsible for cramps and increased myalgias on exertion. The denervation atrophy frequently seen in EMS probably is caused by toxic or ischemic peripheral nerve injury. Edema of skin and other soft tissues probably is due to endothelial damage and inflammation of microvessels, resulting in increased vascular permeability.

Association of EMS with ingestion of L-tryptophan was a striking discovery [59,63]. Epidemiologic analyses showed a remarkably high prevalence of L-tryptophan use in 1989 and demonstrated that the EMS outbreak resulted from ingestion of a chemical constituent that, in turn, was associated with specific tryptophan-manufacturing conditions at one company [63]. The L-tryptophan lots ingested by case patients were produced with use of a new strain of *Bacillus amyloliquefaciens* (strain V) for fermentation in a purification process that employed reduced quantities of powdered carbon. High-performance liquid chromatography demonstrated an absorbance peak (peak E) in the implicated lots to a greater degree than in control lots [64,65]. The structure of peak E was subsequently shown to be 1,1'-ethylidenebis[tryptophan] [64,65]. However, it is still not clear whether this contaminant is a marker or the cause of the epidemic.

Resembling EMS, TOS was linked to consumption of adulterated rapeseed oil distributed in the industrial belt around Madrid [66]. Patients had pruritic, erythematous skin lesions, persisting for up to 4 weeks, followed during the next 2 months by subcutaneous edema (mainly of the extremities), myalgias, arthralgias, contractures, and peripheral blood eosinophilia. Over many years, patients developed indurated plaques of the pretibial areas and occasionally the forearms and abdomen, with marked fibrosis extending into subcutaneous fat [66]. Eosinophil infiltration and degranulation were prominent especially in the acute phase of TOS, and serum eosinophil granule protein levels were elevated during all phases [67].

Eosinophils are associated with other fibrotic reactions, including those resulting from parasitic infections, pulmonary or hepatic drug-sensitivity reactions, and in eosinophilic fasciitis [68]. Eosinophilic fasciitis usually presents with pain, erythema, swelling, and induration of the extremities, as well as peripheral blood eosinophilia and hypergammaglobulinemia [69]. Contractures and rippling of the skin may develop. There is infiltration of lymphocytes, plasma cells, mast cells, and eosinophils, as well as increased thickness of the fascia. Eosinophils elaborate mediators that degrade collagen and stimulate dermal fibroblast DNA synthesis and matrix production [70]. MBP and EPO stimulate respiratory epithelial cells to produce profibrotic cytokines, raising the possibility that cells such as keratinocytes might respond similarly [70].

Cutaneous diseases associated with eosinophilia

The distinctive tinctorial properties of eosinophil granules give these cells a prominence in stained tissue sections that contrasts with their lack of diagnostic power and undefined role in pathogenesis. Eosinophils may be seen in skin biopsy specimens from patients with a variety of inflammatory and neoplastic disorders (Box 3), but they are among the diagnostic criteria in a limited number of cutaneous diseases, including Wells' syndrome, Kimura's disease, angiolymphoid hyperplasia with eosinophilia, and eosinophilic pustular folliculitis [71]. Eosinophils also are prominent in immunobullous diseases, particularly pemphigoid.

Wells' syndrome

Wells' syndrome, also termed *eosinophilic cellulitis*, occurs mainly in adults but also may afflict children [72]. Cutaneous edema is characteristic of the disease [71–81] and was the common clinical feature of the first four patients reported by G. C. Wells in 1971 [76]. The four originally

Box 3. Eosinophils in cutaneous diseases

Angiolymphoid hyperplasia with eosinophilia

Arthropod bites and sting reactions

Bullous dermatoses

- Pemphigoid
- Pemphigus
- Incontinentia pigmenti

Dermatoses of pregnancy

Drug reactions

Edema

- Angioedema
- Urticaria

Eosinophilic pustular folliculitis

Hypereosinophilic syndromes

Infestations/parasitic diseases

Kimura's disease

Lymphoma

Vasculitis

- Churg-Strauss syndrome
- Eosinophilic vasculitis

Wells' syndrome (eosinophilic cellulitis)

Data from Stetson CL, Leiferman KM. Eosinophilic dermatoses. In: Bologna JL, Jorizzo JL, Rapini RP, et al, editors. *Dermatology*. 2nd edition. St. Louis: Mosby, in press.

reported patients had recurrent edematous infiltrative plaques resembling cellulitis at onset and, later, morphea [75]. The disease typically begins with prodromal cutaneous burning or itching, followed by erythema and edema, sometimes in annular or arcuate plaques or nodules. Over several days, lesions evolve into edematous plaques with violaceous borders, sometimes with bullae. The color may gradually change from bright red to brown-red and then to blue-gray or greenish-gray, resembling the fibrotic condition morphea. Uncommon presentations include papules, vesicles, and hemorrhagic bullae. Single or multiple lesions typically involve the extremities and, less often, the trunk. Wells' syndrome usually resolves within weeks to months, without scarring, but recurrences are common. Lesions typically improve after administration of systemic glucocorticoids. For mild disease, topical glucocorticoids may be sufficient.

Skin lesions are characterized by dermal infiltration of eosinophils, histiocytes, and foci of amorphous and/or granular material in association with connective tissue fibers, termed *flame figures* [75]. In early stages, there is dermal edema; later, histiocytes palisade around flame figures. Extracellular deposition of toxic granule proteins in lesions [80] is evidence that eosinophil degranulation contributes to flame figure formation. Approximately 50% of patients have peripheral blood eosinophilia [82]. The severity of skin lesions appears to vary with serum levels of IL-5 and ECP [83], and IL-5 is implicated in hereditary eosinophilic cellulites [82].

Reports of flame figures in lesions from patients with a spectrum of diseases indicate that flame figures are characteristic for, but not diagnostic of, Wells' syndrome [84]. Whether Wells' syndrome is a specific disease triggered by underlying factors such as infection and drugs or a reaction pattern is difficult to ascertain from the literature and clinical experience [84]. Wells' syndrome has been observed in patients with HES [35,36], in addition to a variety of other disorders. Associations with arthropod bites [75,78,85], parasitic infection (onchocerciasis) [86], dental abscess, mastocytoma [87], myeloproliferative disease [87], colon cancer [88], Churg-Strauss syndrome [77], dermatographism [89], herpes simplex infection [90], immunobullous disease [75,91], and drug reaction [92,93] suggest that the syndrome is a reactive or hypersensitivity phenomenon [73].

Kimura's disease

In 1948, Kimura and colleagues [94] described "unusual granulation combined with hyperplastic changes in lymphatic tissue" associated with regional lymphadenopathy. Kimura's disease (KD) occurs predominantly in young adult Asian males. Patients have solitary or several asymptomatic, typically chronic and recurrent, nontender, slowly growing subcutaneous nodules that tend to involve the head and neck but may be localized to the extremities, axillae, groin, or trunk. Overlying skin usually appears unaffected. Regional lymphadenopathy is common, and some patients have

widespread lymph node enlargement [95,96]. Approximately 16% of KD patients have associated renal disease, including glomerulonephritis and nephrotic syndrome [97].

Peripheral blood eosinophil counts and serum IgE levels are elevated in most patients. Lesions are characterized by lymphoid aggregates, usually lymphoid follicles with germinal centers, numerous eosinophils, and fibrosis; the pattern may include eosinophil abscesses. The combination of peripheral blood eosinophilia, elevated serum IgE level, and histologic findings of lymphoid nodules with numerous eosinophils suggests that KD represents a hypersensitivity reaction.

Angiolymphoid hyperplasia with eosinophilia

Originally described as “subcutaneous angiolymphoid hyperplasia with eosinophilia” [98], angiolymphoid hyperplasia with eosinophilia (ALHE) occurs in both males and females, usually in the third to fifth decade of life. In contrast to KD, which develops mainly in Asians, ALHE has no racial predilection. There may be a history of trauma. Lesions are erythematous, violaceous, or brown papules, plaques or nodules of the dermis and/or subcutaneous tissues, that typically involve the head and neck region. They may be solitary, few, or multiple; pruritic, painful, or pulsatile; and tend to be chronic, without remission.

The dominant histologic feature is a well-defined area in the dermis and/or subcutaneous fat of prominent vascular proliferation with large epithelioid or histiocytoid endothelial cells that contain abundant eosinophilic cytoplasm, often with cytoplasmic vacuoles. There are variable numbers of eosinophils and lymphocytes [99], and occasional lymphoid nodules. Approximately 20% of patients have peripheral blood eosinophilia; IgE levels are unremarkable. ALHE may represent a form of arteriovenous shunt [100]. It is considered a reactive phenomenon, possibly developing in response to or in association with an underlying vascular malformation.

Whether ALHE and KD represent separate entities or are part of a single disease spectrum has been debated. The distinction is further blurred by a report of KD and ALHE in the same patient [101]. Both diseases are characterized by persistent lesions that usually involve the head and neck, but each has distinct clinical and histologic features. Although eosinophils may be part of the histologic pattern in both diseases, lymphoid follicles with germinal centers dominate KD, and vascular proliferation with large epithelioid endothelial cells characterizes ALHE. Lesional tissue and peripheral blood eosinophilia are more striking in KD.

Eosinophilic pustular folliculitis

There are three clinical types of eosinophilic pustular folliculitis (EPF) [102]. First reported by Ofuji in 1965, classical EPF is not restricted to

Asians but typically occurs in Japanese individuals during the third to fourth decades of life [103]. Classical EPF is characterized by an annular distribution of recurrent crops or clusters of follicular papules and pustules, which usually resolve in 7 to 10 days. Lesions predominantly involve the face and trunk but may affect the extremities, including palms and soles [103]. In contrast, the second type of EPF, HIV-associated EPF, tends to have an urticarial quality and presents as extremely pruritic discrete follicular papules, typically involving the head, neck, and proximal extremities [104,105]. Described initially in 1986, HIV-associated EPF is now recognized as the most common type. The third type, EPF of infancy, presents during the first year of life; it involves the scalp but also may affect the face and extremities [102,103,105]. EPF of infancy typically resolves completely, while classical and HIV-associated EPF are recurrent. EPF also has been found in association with lymphoma, leukemia, polycythemia vera, and myelodysplastic syndrome, and drug-induced EPF [106] has been reported.

Histologically, the most striking aspect of EPF is infiltration of eosinophils into hair follicles and perifollicular zones, sometimes with follicular damage. Peripheral blood eosinophilia is present in all three types of EPF. Classical EPF patients usually have eosinophilia with leukocytosis, whereas eosinophilia with lymphopenia is a feature of HIV-positive patients. Low CD4 cell counts and high IgE levels are typical of HIV-associated disease [107]. Topical glucocorticoids generally are used first for the treatment of all types of EPF. Nonsteroidal anti-inflammatory drugs, particularly indomethacin, are another first-line therapy; clinical improvement may be observed within 2 weeks and is associated with a decrease in peripheral blood eosinophil counts [108]. Antiretroviral treatment, with resultant increase in CD4 cell counts, often is associated with improvement in HIV-associated EPF, although lesions may develop during antiretroviral therapy.

Autoimmune blistering diseases

Patients with autoimmune blistering diseases often have peripheral blood eosinophilia and prominent infiltration of eosinophils. In 1968, Emmerson and Wilson-Jones [109] introduced the term eosinophilic spongiosis in their report of pemphigus patients who had skin biopsy specimens that showed infiltration of the epidermis with eosinophils and intraepidermal vesicles containing eosinophils. Among the pemphigus subtypes, eosinophilic spongiosis occurs most frequently in pemphigus vulgaris [110]. However, eosinophilic spongiosis is now considered to be a marker more often of bullous pemphigoid (BP) than pemphigus, particularly when patients present with urticarial lesions. Eosinophilic spongiosis also is a feature of other types of pemphigoid, including pemphigoid (herpes) gestationis, and has been noted in lesions of incontinentia pigmenti, acute dermatitis, arthropod bites and incidentally in other disorders. Peripheral blood eosinophilia is variable in these conditions but can be in the HES range.

BP occurs predominantly in older individuals and is characterized clinically by tense cutaneous blisters arising on pruritic, urticarial bases. Blisters also may arise on a background of macular erythema or on normal-appearing skin. Tense blisters or erosions may involve mucosa. In addition to marked peripheral blood eosinophilia, autoantibodies, predominantly IgG class, develop to basement membrane zone (BMZ) antigens. Recently, IgE BMZ antibodies have been implicated in the pathogenesis of BP [111,112].

In addition to eosinophilic spongiosis, lesions of BP show a variable inflammatory cell infiltrate that typically contains eosinophils scattered throughout the upper dermis or clustered at the edge of dermal-epidermal separation. Eosinophils often are present in the blister space, and eosinophil degranulation is massive, with extensive tissue deposition of MBP [113]. Blister fluid contains both MBP and ECP. Deposition of eosinophil granule MBP is associated with blister formation in a related disease, pemphigoid gestationis [114], in the genodermatosis incontinentia pigmenti [115], in blisters of Churg-Strauss syndrome [57] and in bullous morphea [116]. Adhesion molecule expression in lesional tissue, as well as IL-3 and IL-5 in blister fluid, likely contribute to eosinophil activation in pemphigoid [113]. Eosinophils elaborate the 92-kd gelatinase matrix metalloproteinase 9 [117], which probably contributes to dermal-epidermal separation in BP; it is produced by eosinophils at the site of blister formation and has been shown to cleave the extracellular domain of the recombinant 180-kd BP autoantigen, a transmembrane component of the basement membrane zone [117]. There are reports of patients with T cell lymphoma who develop BP, particularly following UV light (UVL) treatments [118]. UVL may induce damage that exposes basement membrane zone antigens and (in conjunction with clonal T cells that generate T helper 2 cytokines IL-4 and IL-5) production of BMZ antibodies ensues. T cell activity in general may be a cofactor with UVL, because pemphigoid has long been associated with psoriasis and UVL treatment [119,120] and also has been reported in UVL-treated morphea [121].

Clinical reaction patterns with eosinophils

There are a variety of cutaneous diseases, with or without associated peripheral blood eosinophilia, in which eosinophil infiltration may be a histologic feature, but either the pattern is unremarkable or eosinophils are not critical for the histologic diagnosis. In many of these dermatoses, eosinophils lose their morphologic integrity after cytolytic disruption and are not identifiable histologically. However, toxic granule proteins and other eosinophil products are deposited in skin and persist for extended periods [23].

Although parasitic infestations typically are associated with eosinophils, the histologic pattern is not diagnostic unless a specific organism is identified in tissue sections [5,122]. Infection with *Onchocerca volvulus* causes pruritic

dermatitis with lichenification; there is slight infiltration of eosinophils but extensive extracellular deposition of granule proteins throughout the dermis of lesions [123]; after treatment, extracellular granule proteins are located around degenerating microfilariae [5,124]. Although eosinophils are rarely a prominent histologic feature of atopic dermatitis, extensive extracellular dermal deposition of granule proteins is observed in lesions (Fig. 6); even normal-appearing skin may show scant MBP deposition [123,125–127]. Prurigo nodularis [128,129] and pachydermatous eosinophilic dermatitis [130] exhibit a pattern of dermal extracellular granule protein deposition similar to that seen in atopic dermatitis and onchocercal dermatitis. In both atopic dermatitis and prurigo nodularis, eosinophil granule products are deposited around cutaneous nerves and, although the eosinophil is not recognized as an inducer of itch, there is evidence that eosinophils play a role in itch provocation [131–134].

In addition to pemphigoid gestationis, several other pruritic dermatoses of pregnancy may exhibit tissue eosinophils and peripheral blood eosinophilia [97,135,136]. Polymorphic eruption of pregnancy [137], previously called pruritic urticarial papules and plaques of pregnancy [138], presents in the third trimester with erythematous urticarial lesions involving the abdomen, thighs, buttocks, and upper limbs. Papular dermatitis of pregnancy [139] is an eruption of generalized extremely pruritic wheal-like papules, and autoimmune progesterone dermatitis [140], presents early in pregnancy as follicular and perifollicular papules and pustules predominantly involving the extremities, with the histologic finding of numerous eosinophils (with eosinophil abscesses) in follicles, epidermis, dermis and subcutaneous fat.

Eosinophil granule proteins are toxic to many cell types including endothelial cells, which implicates them in the development of vasculitis, including Churg-Strauss syndrome [57,141,142]. Eosinophils often are

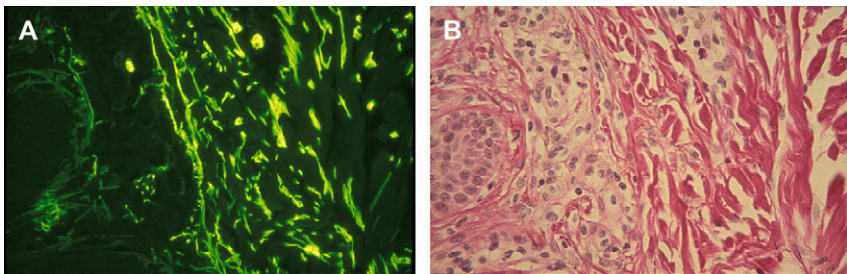


Fig. 6. Atopic dermatitis. (A) Skin biopsy section stained for eosinophil granule MBP shows extensive extracellular deposition in the dermis with cellular staining of only three eosinophils (original magnification $\times 400$). (B) Hematoxylin-eosin counterstain of the A section shows chronic inflammation (original magnification $\times 400$). (From Leiferman KM, Ackerman SJ, Sampson HA, et al. Dermal deposition of eosinophil-granule major basic protein in atopic dermatitis. Comparison with onchocerciasis. *N Engl J Med* 1985;313:283; with permission. Copyright ©1985 Massachusetts Medical Society. All rights reserved.)

associated with cutaneous allergic drug reactions and urticarial vasculitis. When eosinophils are part of the histologic pattern in leukocytoclastic vasculitis, the eruption is probably drug-induced [143]. Associated with peripheral blood eosinophilia, eosinophilic vasculitis is characterized by widespread chronic, recurrent, pruritic, erythematous, purpuric papules as well as angioedema of the face and hands; the histologic pattern consists of necrotizing small vessel vasculitis with prominent infiltration of eosinophils [141]. Eosinophilic vasculitis may be idiopathic or associated with connective tissue disease [142], Raynaud's phenomenon, or HES [33].

Management

Management is guided by the diagnosis of HES and/or associated diseases. General diagnostic criteria for HES are reviewed by Sheikh and Weller elsewhere in this issue. Obtaining skin biopsies is important, including specimens for histologic evaluation, direct immunofluorescence (DIF) testing, and immunophenotyping. In addition to routine hematoxylin-eosin-stained sections, special stains may be useful. Immunobullous disease, presenting with or without blisters, can be diagnosed by DIF. Immunostains for MBP or other granule proteins can help establish eosinophil involvement when few or no infiltrating eosinophils are present. Giemsa, toluidine blue, and/or tryptase stains will identify mast cells. Immunophenotyping of lymphocytes in cutaneous tissue sections may aid the diagnosis of lymphocytic HES. To detect T cell or B cell clones, skin biopsy tissue also can be subjected to lymphocytflow and evaluated for T cell receptor and light chain gene rearrangements.

The treatment goal for patients with HES is relief of symptoms and improvement in organ function, while keeping peripheral blood eosinophils at 1000–2000/ μ L and minimizing side effects [3]. Symptomatic relief is especially important for patients who present with debilitating skin involvement. Moreover, cutaneous lesions and symptoms may reflect underlying disease activity in HES. Therefore, monitoring response of the skin to treatment may be helpful in judging systemic therapeutic efficacy. Myeloproliferative HES is very responsive to imatinib, which usually induces hematologic remission. In the absence of the FIP1L1-PDGFR α genetic mutation, and after *Strongyloides* infection has been excluded [144], first-line therapy is systemic glucocorticoids. Approximately 70% of patients will respond to prednisone, with peripheral eosinophil counts returning to normal. Patients who fail glucocorticoid monotherapy generally have a worse prognosis; in such cases, or when long-term side effects become problematic, other treatments should be used. Patients with features of myeloproliferative HES, but who are FIP1L1-PDGFR α -negative, still may respond to imatinib [41]. Interferon- α has been beneficial in both myeloid and lymphocytic HES types [145]. Other treatment options include: hydroxyurea, dapsone, vincristine sulfate, cyclophosphamide, methotrexate, 6-thioguanine, 2-chlorodeoxyadenosine

and cytarabine in combination, pulsed chlorambucil, etoposide, cyclosporine, intravenous immunoglobulin, alemtuzumab, and psoralen ultraviolet A phototherapy [146], extracorporeal photochemotherapy alone or in combination with interferon- α or other therapies, as well as bone marrow and peripheral blood stem cell allogeneic transplantation [147,148]. Two monoclonal antibodies against human IL-5 have been associated with clinical improvement, including decrease in cutaneous symptoms, and reductions in peripheral blood and dermal eosinophils, particularly in patients with lymphocytic HES [46].

Summary

Eosinophils have many biologic effects in skin and other tissues, most of which appear to be deleterious. Eosinophils are not resident cells of the skin and, therefore, when present, are implicated in cutaneous disease. Their involvement may be difficult to recognize because they degranulate and lose morphologic integrity. Cutaneous lesions associated with eosinophil activities particularly include those characterized by edema, eczema, mucosal ulcers, vasculitis, blisters, and fibrosis. All these eosinophil-associated cutaneous lesions are found in HES. Dermatologic disease involving skin and mucous membranes is an important component of all HES variants and may be the presenting signs of HES. Mucosal ulcers and edema are extremely debilitating and may be difficult to treat. Splinter hemorrhages and/or nail fold infarcts may be initial clues to potentially life-threatening thromboembolic disease. In addition to HES, several skin diseases and inflammatory reaction patterns have prominent eosinophil involvement. Many of these are not typically considered in the context of HES, and the diagnosis may be delayed because eosinophil counts are not determined and followed. Recognition of eosinophil participation in cutaneous and extracutaneous diseases is critical, because eosinophilic endomyocardial disease, which can develop in any eosinophil-associated disorder, may have grave consequences.

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