

Eosinophilia in Dermatologic Disorders



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KEYWORDS

- Eosinophils • Atopic dermatitis • Drug hypersensitivity reaction
- Cutaneous lymphoma • Eosinophilic dermatitis • Hypereosinophilic syndromes

KEY POINTS

- Cutaneous eosinophil infiltration is observed in a broad spectrum of dermatologic disorders including allergic, autoimmune, infectious, and neoplastic diseases and can be associated with blood eosinophilia.
- The clinical presentation of eosinophilic dermatoses varies considerably, but pruritus is a common symptom.
- The diagnosis of eosinophilic dermatoses is usually based on histology, unless clinical signs and symptoms are unmistakable.
- The accumulation of eosinophils in the skin is reactive in most cases owing to the production of eosinophilopoietic cytokines by T cells or tumor/lymphoma cells.
- A potential pathogenic role of eosinophils in skin diseases has been attributed to host defense, immunoregulation, and fibrosis.

DERMATOLOGIC DISORDERS WITH EOSINOPHILIA

The presence of eosinophils in the skin is common in a broad spectrum of cutaneous disorders. To note, the skin lacks eosinophils under physiologic conditions. The clinical presentations of eosinophilic skin diseases are highly variable and include eczematous, papular, urticarial, bullous, nodular, and fibrotic lesions. Pruritus is a unique and striking feature of all of them, although not pathognomonic. In some patients presenting with itchy skin lesions, the disease can easily be diagnosed considering the patient history, age, clinical findings and distribution, for example, atopic dermatitis (AD),

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insect bites, larva migrans infection, and drug reactions. Moreover, inflammatory skin lesions are the most common clinical manifestation of hypereosinophilic syndromes (HES).^{1,2} To confirm or make the correct diagnosis, biopsies from active skin lesions have to be taken for histologic, immunohistochemical, and immunofluorescence investigations, and in some cases polymerase chain reaction analysis to check for clonality of infiltrating cells. Eosinophils can easily be identified by hematoxylin and eosin staining in skin biopsies. Their numbers, localization, and degranulation, as well as tissue damage, might provide diagnostic clues for the dermatopathologist; for example, flame figures in Wells' syndrome, V-shaped eosinophilic infiltrate in arthropod reactions, and eosinophil lining and blister formation at the dermal–epidermal junction in bullous pemphigoid (BP). The eosinophilia can be restricted to the skin, but may be accompanied by blood eosinophilia, for example, in AD, BP and cutaneous T-cell lymphoma (CTCL), and involve other organs as well, such as in a drug reaction with eosinophilia and systemic symptoms (DRESS). Associated blood eosinophilia may be as high greater than $1.5 \times 10^6/L$, as in HES.

PATHOGENIC MECHANISMS MEDIATED BY EOSINOPHILS

Although eosinophils are encountered in many skin diseases, their functional role in the pathogenesis remains largely unclear. There is evidence that eosinophils might contribute to pathogen defense, regulate inflammatory responses, and induce fibrosis/remodeling.^{3,4} According to their cytokine expression, functionally different subpopulations seem to exist: eosinophils that potentially regulate inflammatory responses and/or fibrosis.⁵ Moreover, the cytokine pattern of eosinophils is distinct in allergic reactive, infectious, and autoimmune diseases, as well as in lymphomas/tumors.⁵ Eosinophils have been demonstrated to form extracellular DNA traps (EET) in the skin and thus may play a role in host defense.^{3,6} Thymic stromal lymphopoietin, a cytokine expressed by epithelial cells, for example, in AD and BP, stimulates eosinophils to release EETs that are able to kill bacteria.⁷ Other mechanisms by which eosinophils may release granule proteins are degranulation and cytolysis.^{8,9} In flame figures, granule protein deposition coating collagen fibers can be detected, suggesting a role of eosinophils in tissue damage.¹⁰ Interestingly, tissue damage mediated by major basic protein seems to be limited by extracellular aggregation generating large, nontoxic amyloid plaques.¹¹ In eczematous lesions, a correlation between eosinophils expressing matrix metalloproteinase-9 with interleukin (IL)-17⁺ T cells and remodeling has been reported.¹² Moreover, eosinophils might be involved in causing pruritus, because they can affect skin nerves directly.¹³

CLINICAL PRESENTATIONS OF DERMATOSES WITH EOSINOPHILIA

Eczematous Pattern

Atopic dermatitis

AD is a chronic inflammatory skin disease based on a genetic predisposition. The prevalence is as high as 20% in children and 10% in adults. Typically, AD presents with pruritus and excoriated eczematous skin lesions on the face, neck, and extensor sites of the extremities in infants, and subsequent lichenification at the flexural folds in children and adults (**Fig. 1A**). The pathogenesis is complex, including an impaired skin barrier function that promotes adaptive immune responses to environmental allergens, together with inadequate innate immune responses to microbes followed by colonization of *Staphylococcus aureus* and viral infections.¹⁴ The diagnosis of AD is based on the clinical signs rather than diagnostic procedures, which may identify triggers. Approximately 80% of AD patients have increased total and specific

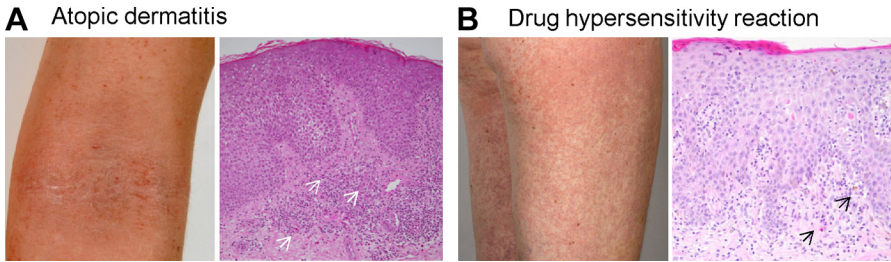


Fig. 1. Clinical presentations and histology of atopic dermatitis and drug hypersensitivity reaction. (A) Lichenification of eczematous lesions in arm fold. Spongiosis and perivascular lymphocytic infiltrate and eosinophils (arrows). (B) Maculopapular exanthema. Dense dermal infiltrate of lymphocytes and eosinophils (arrows) (hematoxylin-eosin, original magnification [A] $\times 100$; [B] $\times 200$).

immunoglobulin (Ig)E to environmental allergens. AD is the first manifestation of atopy preceding allergic rhinitis and bronchial asthma in most patients.

Tissue eosinophilia is a typical finding of AD, often associated with increased blood eosinophil levels and correlating with disease severity.¹⁵ In the skin, eosinophils as part of the perivascular inflammatory infiltrate as well as extracellular granule protein deposits have been identified.^{8,11} So far, the role of eosinophils in the pathogenesis of AD remains uncertain. It seems possible that eosinophils contribute to host defense against invading microbes through the defective skin barrier by generating EET, regulating the immune response, and/or remodeling.^{5,7,12}

The treatment of AD aims to restore the barrier function, for example, by emollients, reduction of inflammation with topical corticosteroids and calcineurin inhibitors, or systemic immunomodulating agents, and avoidance of trigger factors. Successful therapy of acute AD is accompanied by a decrease of eosinophils in blood and skin.^{16,17}

Contact dermatitis

Contact dermatitis (CD), either irritant (ICD) or allergic (ACD), is caused by exogenous triggers and thus manifests at exposure sites, often the hands. ACD develops as a consequence of contact hypersensitivity, usually to low-molecular-weight allergens (haptens), and involves innate and adaptive, predominantly T helper 1 immune responses, in both the sensitization and elicitation phases.¹⁸ In ICD, an exposure to chemicals, wet and/or mechanical work causes damage of the epidermis resulting in a proinflammatory cytokine release by keratinocytes and inflammation.¹⁸ Thus, ICD might pave the way for the development of ACD. The patient's history and clinical signs of acute and/or chronic eczematous lesions are usually diagnostic for CD and biopsies are done for differential diagnosis. Histologic examination shows an inflammatory infiltrate containing eosinophils in the upper dermis and epidermal spongiosis following distinct time courses in ACD and ICD.¹² Eosinophils producing reactive oxygen species were reported to play a role in the development of ICD.¹⁹ Moreover, the numbers of eosinophils correlated with T cells expressing IL-17 and IL-22 known to promote eosinophil recruitment and profibrotic mediator production, suggesting a role in remodeling of eczema.¹² In terms of treatment, avoidance of the triggers is most important. To identify responsible contact allergens, patch tests should be performed.

Scabies and cutaneous larva migrans

Worldwide, secondary eosinophilia is most frequently caused by parasitic diseases, including scabies and larva migrans. Both scabies and hookworm-related cutaneous larva migrans are common in many developing countries and characterized by severe

itching.^{20–23} In scabies, a papular rash is observed. The presence of a linear serpiginous track moving forward in the skin is typical for larva migrans (Fig. 2). Eosinophils and T cells predominate in the infiltrates of scabies and larva migrans infected skin. The diagnosis is based on clinical signs and exposure as well as dermatoscopic and microscopic identification of scabies mites. Scabies can be treated with topicals (eg, permethrin 5%) or with systemic ivermectin (200 µg/kg in a single dose).²⁴ Cutaneous larva migrans is treated typically with single-dose oral albendazole or ivermectin or the topical application of thiabendazole.²²

Primary cutaneous T-cell lymphoma

Mycosis fungoides (MF) and Sezary syndrome (SS) are epidermotropic forms of CTCL characterized by cutaneous infiltration of malignant, clonally expanded T cells.²⁵ Clinical signs of MF are well-defined, often pruritic erythematous patches in non-sun-exposed areas that may evolve to infiltrated plaques and tumors (Fig. 5A).²⁶ SS presents with an erythroderma, severe pruritus, atypical T cells in the peripheral blood, and lymphadenopathy.²⁶ Recently, it has been demonstrated that the malignant cells resemble central memory T cells in SS, and effector memory T cells in MF. These observations are consistent with clinical behavior and responsiveness to therapy as well as comparative genomic hybridization and gene expression profiling data.²⁷ MF and SS have been associated with a T helper 2 cytokine milieu including IL-5 leading to eosinophilia in skin and peripheral blood.

Lymphocytic variant of hypereosinophilic syndromes

Patients with hypereosinophilia owing to T cells with an aberrant immunophenotype present with severe pruritus and often widespread erythematous to erythrodermic skin lesions.^{28,29} The aberrant T cells frequently produce IL-5 and/or IL-3 and stimulate the production and accumulation of eosinophils. Skin histology reveals perivascular infiltrates and exocytosis of lymphocytes and eosinophils.²⁹

Langerhans cell histiocytosis

Langerhans cell histiocytosis is a rare disease mainly affecting children and manifests as either restricted (single-system) or extensive (multisystem) type.³⁰ On the skin, scaly, erythematous, seborrhea-like brown to red papules can be observed. The infiltrate of Langerhans cells (LC) that can be identified immunohistochemically by their expression of CD1a and/or CD207, is admixed with various numbers of macrophages, multinucleated giant cells, T cells, and eosinophils. LC were reported to cause eosinophilia either directly by expressing chemokine (c-c motif) ligand (CCL)5 or indirectly by recruiting T cells that produce IL-5.³⁰

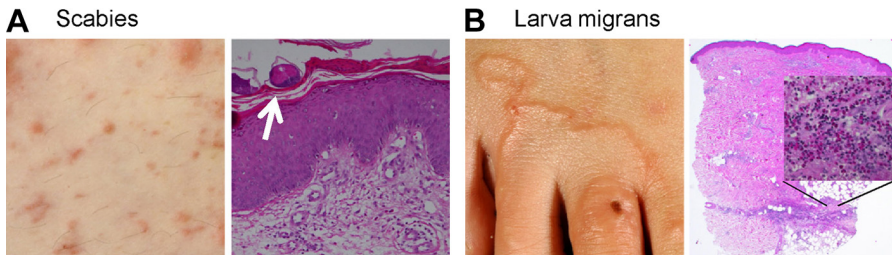


Fig. 2. Clinical presentations and histology of scabies and cutaneous larva migrans. (A) Erythematous excoriated papular and linear lesions. Mites in the horny layer (arrow). (B) Creeping eruption associated with larva migrans. Dense infiltrate of eosinophils in deep dermis and subcutaneous fat (hematoxylin-eosin, original magnification [A] $\times 100$; [B] $\times 10$, insert $\times 100$).

Maculopapular Exanthema

Drug hypersensitivity reactions

Drug hypersensitivity reactions (DHR) are adverse drug reactions to pharmaceutical formulations that clinically resemble allergy, and are dose independent, unpredictable, noxious, and unintended (type B).³¹ According to the onset of symptoms, DHR have been classified in immediate and nonimmediate or delayed reactions. In delayed DHR, most commonly the skin is affected and mainly presents with maculopapular rashes (see Fig. 1B), but also as delayed urticaria, fixed drug eruption, symmetric drug-related intertriginous and flexural exanthema, acute generalized exanthematous pustulosis, toxic epidermal necrolysis, or vasculitis.³¹ It has been hypothesized that drugs directly or after processing by dendritic cells activate T cells that produce cytokines and cytotoxins resulting in tissue damage and an inflammatory response.³¹ Eosinophils can be found among inflammatory cells in the skin and often peripheral blood eosinophil levels are increased.

Drug reaction with eosinophilia and systemic symptoms

An erythematous morbilliform rash in association with systemic organ involvement, such as hematologic, hepatic, renal, pulmonary, cardiac, neurologic, gastrointestinal, or endocrine abnormalities, is the most commonly encountered cutaneous finding of DRESS.³² Eosinophils releasing toxic granule proteins have been implicated in causing tissue damage and thus organ failure.^{33,34} Aromatic anticonvulsants and sulfonamides are the most frequent causes of DRESS occurring 2 to 6 weeks after initiation of therapy.³² In addition to a certain genetic disposition (HLA haplotypes), reactivation of herpesviruses, and immunosuppression play a role in the pathogenesis of DRESS.³² Leukocytosis and hypereosinophilia, as well as increased liver enzymes, urea nitrogen, and creatinine blood levels, are typical findings.³² The culprit drug has to be withdrawn immediately. In addition therapy with corticosteroids, supportive care measures should be initiated.

Urticarial Pattern

Urticaria

Urticaria is a common, mast cell-driven disease presenting with wheals, angioedema, or both (Fig. 3A).³⁵ Acute urticaria is often associated with upper respiratory infections, drugs, or IgE-mediated reactions, and spontaneously regresses within 6 weeks. The pathogenesis of chronic spontaneous urticaria is not understood completely. Mast cell activation might be triggered by infections, allergic and pseudoallergic reactions,

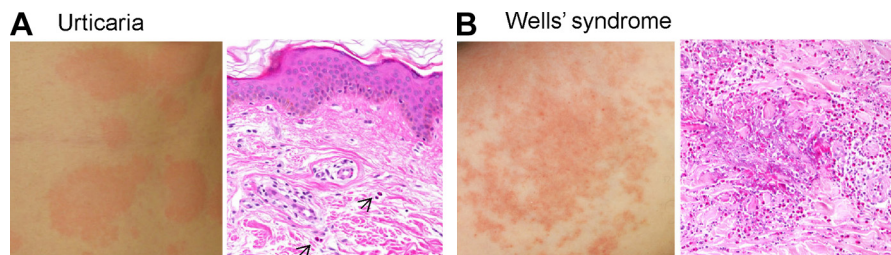


Fig. 3. Clinical presentations and histology of urticaria and Wells' syndrome (eosinophilic dermatitis). (A) Wheals on the trunk, usually persisting less than 24 hours. In the dermis, edema and perivascular mixed infiltrate intermingled with eosinophils (arrows). (B) Persisting urticarial lesions. Flame figure and interstitial infiltration of eosinophils in the dermis (hematoxylin-eosin, original magnification [A] $\times 200$; [B] $\times 40$).

drugs, or autoimmune responses. For inducible forms of urticaria, the triggers, for example, heat, cold, pressure, and ultraviolet light, can easily be identified. Eosinophils are part of the mixed inflammatory infiltrate in an edematous dermis. By releasing tissue factor and inducing an increase of vascular permeability resulting in edema, eosinophils have been assumed to directly contribute to the development of wheals.³⁶

Eosinophilic cellulitis (Wells' syndrome)

Episodes of pruritic dermatitis, persistent urticarial lesions, painful edematous swellings, and occasionally blisters are the clinical manifestations of Wells' syndrome (see Fig. 3B). A skin biopsy shows a dense eosinophilic infiltration of the dermis, degranulation, and flame figures.³⁷ Wells' syndrome has been classified as an organ restricted eosinophilic disorder among HESs.³⁸

Episodic angioedema with eosinophilia (Gleich's syndrome)

Among the HES, this rare disease has been classified as undefined, episodic variant. In 1984, Gleich and colleagues³⁹ reported 4 patients with recurrent attacks of angioedema, urticaria, and fever, transient increase of body weight of up to 18%, and increased leukocyte counts without any inner organ dysfunction that could be controlled by corticosteroids. Recently, a multilineage cell cycling in association with the presence of aberrant and/or clonal T-cell populations has been reported in episodic angioedema with eosinophilia.⁴⁰ In skin biopsies, increased numbers of eosinophils and mast cells were observed during attacks, suggesting a role for both cell types in the pathogenesis of angioedema.⁴⁰

Pregnancy-related diseases

Atopic eruption (including eczema, prurigo, papular dermatitis, and pruritic folliculitis of pregnancy) and polymorphic eruption (including pruritic urticarial, toxic erythema, toxemic rash, and late-onset prurigo of pregnancy) are the most common dermatoses of pregnancy distinguished from pemphigoid gestationis and intrahepatic cholestasis of pregnancy by morphology, onset, and (immune-)histologic findings.⁴⁰ All of them are accompanied by severe pruritus. Prominent tissue eosinophilia was observed in prurigo, polymorphic eruption, and eczema of pregnancy.⁴¹

Cutaneous mastocytosis

Cutaneous mastocytosis, also referred to as urticaria pigmentosa, is a rare disease that may be limited to the skin, but can be a manifestation of indolent, smoldering, and aggressive systemic mastocytosis.⁴² Histopathologically, cutaneous mastocytosis is characterized by aggregates of mast cells in the dermis, whereas eosinophil infiltration is an uncommon finding.⁴³ In KIT D816V-associated systemic mastocytosis with eosinophilia, cutaneous manifestation has been observed in 58% of the patients.⁴⁴

Blisters and Pustules

Bullous pemphigoid

BP, the most common autoimmune subepidermal blistering disease, is characterized by tissue-bound and circulating antibodies to the hemidesmosomal antigens BP180 (BPAG2, type XVII collagen) and BP230 (BPAG1).^{45–47} Patients, typically in their late 70s, present with pruritus and urticarial erythema with tense blisters on the trunk and extremities (Fig. 4A).^{46–48} Blood eosinophilia and dermal infiltrates consisting predominantly of eosinophils are observed in the majority of BP patients.^{41–44} Using direct immunofluorescence techniques, deposition of IgG and/or C3, and in some cases IgE, along the basement membrane zone can be found.^{47,48} In blister fluid and lesional

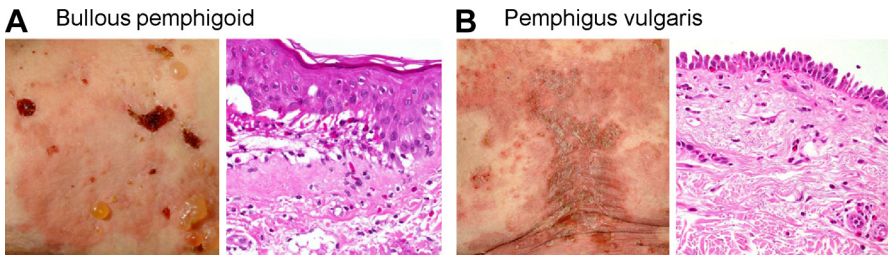


Fig. 4. Clinical presentations and histology of autoimmune blistering diseases: bullous pemphigoid and pemphigus vulgaris. (A) Erythematous lesions with dense blisters and erosions. Subepidermal blister and eosinophils in dermis and blister. (B) Eroded blisters and crusted lesions on erythematous base. Suprabasal acantholysis, mild dermal infiltrate, and scattered eosinophils (hematoxylin-eosin, original magnification [A] $\times 200$; [B] $\times 200$).

skin, several proteolytic enzymes are detected, including plasmin, matrix metalloproteinase-9, and neutrophil elastase, which are strongly expressed by neutrophils and eosinophils.^{47,48} Increased levels of the cytokine IL-5 and the CCL 11 (eotaxin-1) and CCL5, important for eosinophil activation and attraction, have been detected in blister fluids.^{46,47} Because of the potential side effects of systemic corticosteroids currently used for first-line treatment, novel therapeutic options, such as, inhibitory monoclonal antibodies directed against IL-5 and eotaxin, are of increasing interest.^{45,48} Promising results have been reported with rituximab, a potent B-cell-depleting monoclonal antibody.^{45,49}

Pemphigus group

Other autoimmune bullous diseases associated with eosinophil infiltration in the skin are those assigned to the pemphigus group. They are characterized by intraepithelial acantholysis owing to autoantibodies against cell-cell cohesion proteins resulting in blister formation and erosions in pemphigus vulgaris, and papillomatous oozing vegetations of large skin folds and erosions of the oral mucosa as in pemphigus vegetans (see Fig. 4B).^{50,51} Eosinophil exocytosis and eosinophil abscesses have been reported to be common histopathologic findings in pemphigus vegetans.⁵¹

Incontinentia pigmenti

Incontinentia pigmenti is an X-linked dominant multisystem disease affecting ectodermal tissues caused by mutations of the *NEMO* gene. The first vesicobullous stage is characterized by acanthosis, keratinocyte necrosis, epidermal spongiosis, and eosinophil accumulation, and is followed by the verrucous, hyperpigmented, and hypopigmented stages.⁵² IL-1 production by mutant keratinocytes gives rise to tumor necrosis factor- α synthesis by neighboring wild-type cells that in turn induce death and clearance of the mutant cells.⁵³ The expression of eotaxin by keratinocytes correlated with epidermal eosinophil infiltration; however, their pathogenic role has not been defined to date.⁵²

Eosinophilic pustular folliculitis

Eosinophilic pustular folliculitis (EPF) is an inflammatory skin disease characterized by papulopustular eruptions forming annular plaques. Biopsies show spongiosis of hair follicle epithelium with infiltration of eosinophils and lymphocytes, forming eosinophilic follicular pustules that are a typical diagnostic feature.^{54–56} In addition to classical EPF, mainly found in Japan, infancy-associated EPF and immunosuppression-associated EPF in the setting of human immunodeficiency virus infection and malignancies

have been described. Classical EPF predominantly affects the face and trunk, and infancy-associated EPF the scalp. Immunosuppression-associated EPF lacks face predilection and annular arrangement of lesions.^{54,56} Eosinophilia and increased levels of IgE can be observed in EPF patients.⁵⁴ Eotaxin-1 (CCL11), a potent eosinophil attractant, and T helper 2 type cytokines such as IL-13, IL-4, and IL-5, are considered important in the eosinophil recruitment and activation in human immunodeficiency virus-associated EPF.⁵⁵ Recently, it has been shown that prostaglandin D2 stimulates sebocytes to produce eotaxin-3 (CCL26), a chemoattractant for eosinophils, inducing eosinophil accumulation in the pilosebaceous unit.^{55,56} This is in line with the observation that inhibitors of cyclooxygenases involved in prostaglandin synthesis are effective in treating EPF.⁵⁵

Nodular Lesions

Prurigo nodularis

Symmetrically distributed, firm, hyperkeratotic nodular lesions on the extensor surfaces of the extremities induced by extreme chronic pruritus and permanent scratching are the hallmarks of prurigo nodularis (PN), mainly affecting middle-aged woman.⁵⁷ The histologic analysis of PN lesions revealed an eosinophil infiltration in approximately 50%.⁵⁷ How eosinophils are involved in the pathogenesis of PN, possibly by inducing pruritus and/or stimulating fibrosis, remains to be elucidated.

Granuloma faciale

Granuloma faciale is a rare, benign inflammatory skin disease presenting with persistent red-brown plaques and nodules on the face that grow slowly.⁵⁸ Extrafacial lesions may occur.⁵⁴ To rule out other diagnoses, such as, lupus pernio, lupus vulgaris, lymphoma, discoid lupus erythematosus, and infections, a biopsy has to be taken. Interestingly, there are no granulomas but rather an eosinophil and neutrophil predominant infiltrate and small vessel vasculitis can be observed in the dermis with a typical grenz zone.⁵⁸ A local IL-5 production by T cells most likely contributes to eosinophil infiltration.⁵⁹

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

Palpable purpura and nodules that may undergo necrotic ulceration located on the limbs and scalp are prominent skin manifestations of the vasculitic phase of EGPA.⁶⁰ In the pathogenesis, both T helper 2 responses followed by ANCA production and eosinophil activation, as well T helper 1/T helper 17-mediated granuloma formation and vasculitis are thought to play a role in tissue damage.⁶⁰ In the eosinophilic phase, an extravascular tissue infiltration by eosinophils of virtually any organ, in particular lung, heart, and the gastrointestinal tract, has been observed. Eosinophilic infiltration and fibrinoid necrosis of small to medium-sized vessel walls are characteristic of the vasculitis phase affecting mainly the nervous system, kidneys, and skin.⁶⁰

Angiolymphoid hyperplasia with eosinophilia and Kimura's disease

Angiolymphoid hyperplasia with eosinophilia (ALHE) is a rare disease presenting with unilateral erythematous papules and nodules predominantly in middle-aged woman.⁶¹ Histologic examination shows an increased number of blood vessels with proliferation of endothelial cells possessing pathognomonic cytoplasmic vacuoles and a diffuse lymphocytic infiltrate with eosinophils. Kimura's disease (KD) is a benign reactive lymphoid proliferation, characterized by deep subcutaneous and intramuscular swellings and regional lymphadenopathy predominantly seen in young Asian men.⁶¹ ALHE shares similarities with KD lesions predominantly in the head-neck region, benign and recurrent disease course, and eosinophil-rich lymphoid hyperplasia.⁶¹ In contrast with

AHLE, KD is associated typically with peripheral blood eosinophilia, increased serum IgE levels, and lymphadenopathy. Although the cause of both ALHE and KD is not known, the localization of lesions, lymphoid infiltration, and the presence of eosinophils are suggestive of a reactive reaction possibly to an infectious agent.⁶¹

Primary cutaneous CD30⁺ lymphoproliferative disorders: lymphomatoid papulosis and primary cutaneous anaplastic large-cell lymphoma

Characteristically, lymphomatoid papulosis (LYP) follows a chronic disease course with recurrent development of papulonodular lesions that undergo spontaneous regression after weeks or months (see Fig. 5B).⁶² Primary cutaneous anaplastic large-cell lymphoma (PCALCL) comes with solitary or grouped, rapidly growing and ulcerating, large tumors or thick plaques.⁶² The histology shows large pleomorphic and anaplastic tumor cells intermingled with small lymphocytes, eosinophils, and histiocytes. CD30⁺ lymphomatoid papulosis has an excellent prognosis. Because the risk to develop second cutaneous or nodal lymphoid malignancies is increased, staging is recommended if clinical examination or laboratory tests are suggestive of extracutaneous disease. For treatment of PCALCL, surgical excision or radiotherapy has been recommended. For LYP, a wait-and-see strategy is suggested; otherwise, ultraviolet light therapy, methotrexate, topical steroids and immunomodulators, and retinoids have been recommended.⁶²

Cutaneous B-cell lymphomas

To diagnose and classify cutaneous B-cell lymphoma (CBCL) and distinguish them from secondary skin involvement by a systemic lymphoma, a careful morphologic and immunohistochemical analysis and staging are required.⁶³ According to the cells of origin, CBCL are classified in primary cutaneous follicle-center lymphoma (PCFCL), primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL, LT), and primary cutaneous marginal zone lymphoma (PCMZL). They present with solitary patches and tumors of the trunk and head-neck area in PCFCL, rapidly growing tumors on the legs in PCDLBCL, and multifocal patches, plaques or nodules on trunk and arms in PCMZL.⁶³ It has been demonstrated that an aberrant expression of the B-cell lymphoma-6 transcriptional repressor protein via regulation of the transcription factor GATA-3 promotes a T helper 2-type inflammation that subsequently might trigger eosinophilia.⁶⁴

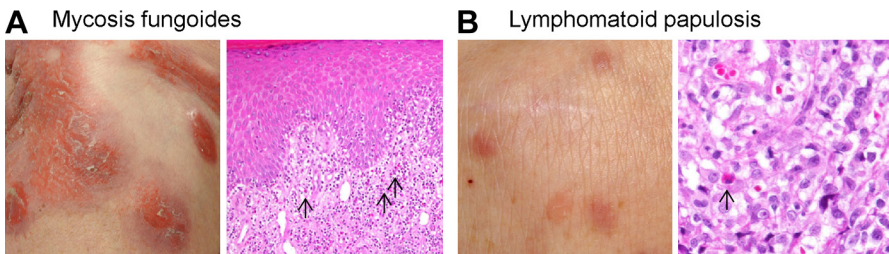


Fig. 5. Clinical presentations and histology of nodular lesions in mycosis fungoides, a cutaneous T-cell lymphoma, and lymphomatoid papulosis, a primary cutaneous CD30⁺ lymphoproliferative disorder. (A) Patches and nodular lesions. Dense infiltrate of lymphocytes and some eosinophils (arrows) in the dermis with exocytosis of lymphocytes. (B) Papular and nodular erythematous-brownish lesions. Mixed cellular infiltrate of large atypical cells with few admixed small lymphocytes, eosinophils (arrow), neutrophils, and histiocytes (hematoxylin-eosin, original magnification [A] $\times 100$; [B] $\times 400$).

Hodgkin's lymphoma

Cutaneous specific manifestations of Hodgkin's lymphoma (HL) clinically present as reddish-brown papules, plaques, nodules, and ulcerated tumors sharing the same histologic findings with the nodal counterpart.⁶⁵ Hodgkin/Reed Sternberg tumor cells were shown to induce tumor necrosis factor- α -mediated eotaxin production by fibroblasts and thus contribute to the recruitment of eosinophils.⁶⁶ There is increasing evidence that the microenvironment, including eosinophils and their products, promote tumor progression in HL.⁶⁷

Eosinophilic dermatosis of hematologic malignancies

Eosinophilic dermatosis presenting with pruritic, indurated erythematous papules and nodules, and in some cases vesicles and bullae resembling insect bites, on face, trunk and extremities has been reported as a nonspecific cutaneous reaction in patients with hematologic malignancies, mainly chronic lymphocytic leukemia.⁶⁸ Eosinophil infiltration has been observed interstitially in the dermis as well as in the epidermis and subcutis.

Cutaneous features of hypereosinophilic syndromes

The most common manifestations of HESs are dermatologic findings (37%).^{1,2} Splinter hemorrhages and nail fold infarcts owing to thromboembolism can be the first signs of HESs associated with endomyocardial involvement.² In patients with myeloproliferative HESs, severe mucosal ulceration has been observed.²

Fibrosis

Eosinophilic fasciitis

Painful erythematous swelling followed by induration and thickening of the skin associated with blood eosinophilia, hypergammaglobulinemia, and an increased erythrocyte sedimentation rate are suggestive of eosinophilic fasciitis (EF), a rare connective tissue disease of unknown etiology. The diagnosis is based on the histopathology of a deep biopsy. By releasing toxic granule proteins as well as profibrotic mediators, eg, metalloproteinases and tumor growth factor- β , infiltrating eosinophils in the fascia seem to play a direct role in the pathogenesis of EF.⁶⁹ Furthermore, increased levels of IL-5 have been observed in patients with EF.⁷⁰

Localized scleroderma

Thickening of collagen bundles as well as a dense perivascular and periadnexal infiltrate of predominantly lymphocytes together with histiocytes, plasma cells, and eosinophils are typical histologic findings of early lesions of localized scleroderma (LS). Morphea is the most common subtype of LS presenting with oval-shaped lesions with a whitish and sclerotic center surrounded by a lilac ring.⁷¹ Various triggers, such as, drugs, mechanical trauma, *Borrelia* infection, have been discussed as initiators of LS; however, their causative role remains unclear.⁷¹ Morphea-like skin lesions have been reported in eosinophilia myalgia syndrome and toxic oil syndrome characterized by blood hypereosinophilia, disabling myalgias, and multiorgan dysfunction.⁷²

DIAGNOSTIC AND THERAPEUTIC APPROACHES

Dermatologic disorders with eosinophilia usually present with pruritus, but variable morphologies as described often preclude determination of an exact diagnosis. Cutaneous and/or peripheral blood eosinophilia are confirmed by histology of a skin biopsy and differential blood cell count, respectively (Fig. 6). In the first instance, common eosinophilic dermatoses should be considered, such as AD, autoimmune blistering

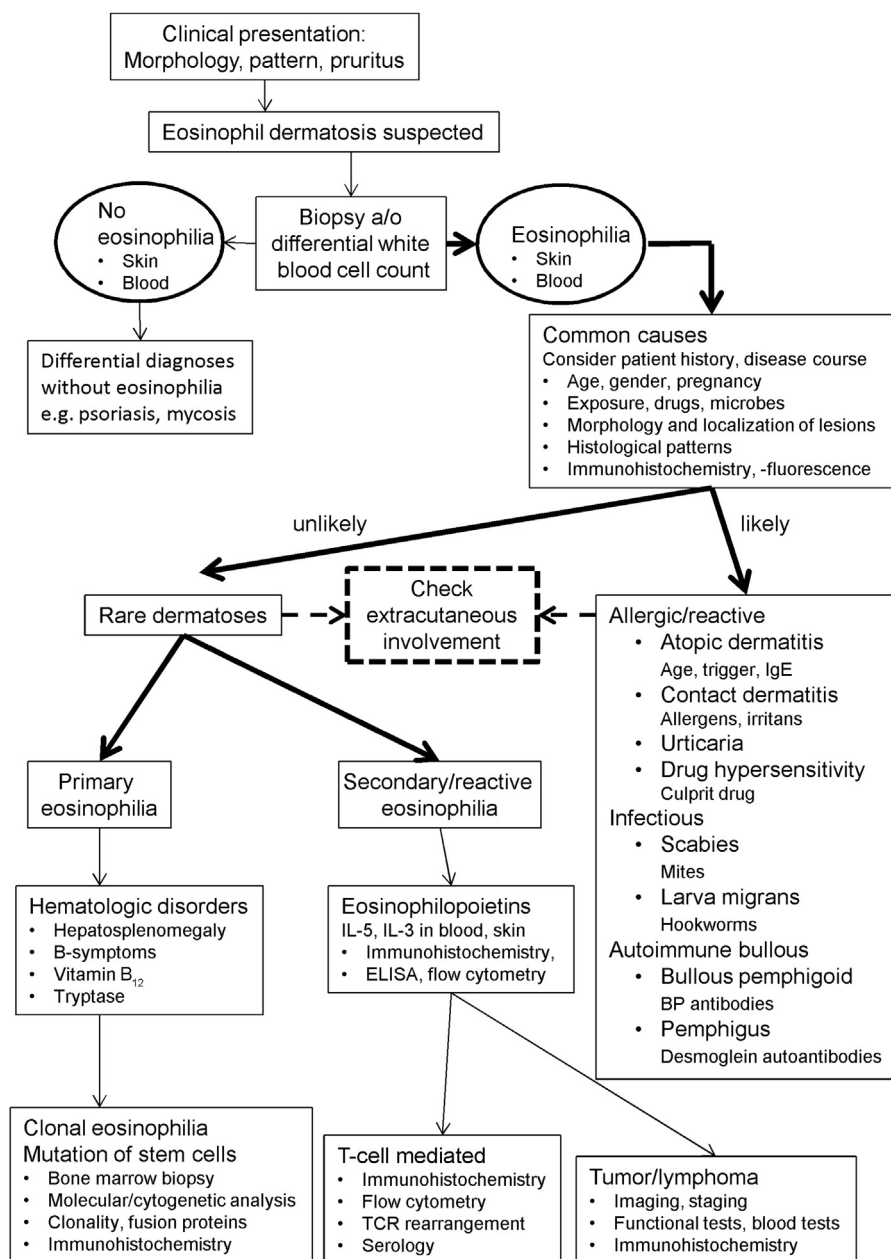


Fig. 6. Diagnostic workup for skin diseases associated with eosinophilia. ELISA, enzyme-linked immunosorbent assay; IgE, immunoglobulin E; IL, interleukin; TCR, T-cell receptor.

diseases, and drug hypersensitivity reactions. To confirm or exclude those, additional serologic tests, immunohistochemical or immunofluorescence tests, and allergy workup have to be done. Furthermore, potential infections, for example, acquired while traveling, should be ruled out. In addition to the patient's history and clinical

examination, the differential diagnosis should be complemented by appropriate laboratory tests and imaging. In addition to the skin, involvement of other organs should be ruled out.

If tissue and/or blood eosinophilia cannot be assigned to a distinct eosinophilic disease, the question of what drives the eosinophilia arises. Principally, 2 main mechanisms causing eosinophilia have been identified.⁷³ (Hyper)eosinophilia may be primary and produced by clonal (neoplastic) eosinophils, or secondary, reactive, owing to an extrinsic cytokine production, for example, by T cells or tumor cells.^{73,74} This discrimination is essential for planning further diagnostic investigations and treatment. Reactive eosinophilia is caused by eosinophilopoietins, such as IL-5 and IL-3 that are produced by T cells or malignant lymphoma/tumor cells. In some cases, aberrant T-cell subsets and clones can be detected, which have to be differentiated from hematopoietic stem cell disorders in which both the eosinophils and lymphocytes belong to the neoplastic clone. To get evidence for or exclude a myeloid neoplasm and thus eosinophil clonality, and molecular and cytogenetic studies should be applied. To exclude an underlying systemic mastocytosis, analyses of KIT (codon 816) mutation and serum tryptase level should be done. For proper diagnostics and treatment of patients with neoplastic (hyper)eosinophilia or tumor- or lymphoma-driven reactive eosinophilia, a cooperation between dermatologists, hematologists and oncologists is mandatory.

Treatment of eosinophilic skin diseases conforms to the underlying pathologic mechanisms.^{75–80} Eosinophilia in inflammatory skin diseases, CTCL, lymphocytic forms of HES are treated with corticosteroids, and other immunosuppressive or immunomodulating drugs. Recently, a significant improvement of AD by blocking IL-4/IL-13 activity has been reported.⁷⁷ Cessation of the culprit drug is mandatory in drug hypersensitivity, whereas infectious diseases require specific antibiotic, antiviral, or antiparasitic therapy. Myeloproliferative disorders and lymphomas are in focus of specific targeted therapies. Anti-IL-5 antibody therapy has been demonstrated to be effective in patients with non-FIP1L1/PDGFRA and clonal T-cell HES, whereas tyrosine kinase inhibitors are indicated in HES owing to the fusion protein FIP1L1/PDGFRA.^{78,79} Patients with SS, a CTCL, respond to an anti-CD52 therapy.⁸⁰ Currently, a number of studies evaluating novel substances targeting eosinophils are ongoing.⁷⁶

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