

Eosinophilic Skin Diseases: A Comprehensive Review

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Abstract Eosinophilic skin diseases, commonly termed as eosinophilic dermatoses, refer to a broad spectrum of skin diseases characterized by eosinophil infiltration and/or degranulation in skin lesions, with or without blood eosinophilia. The majority of eosinophilic dermatoses lie in the allergy-related group, including allergic drug eruption, urticaria, allergic contact dermatitis, atopic dermatitis, and eczema. Parasitic infestations, arthropod bites, and autoimmune blistering skin diseases such as bullous pemphigoid, are also common. Besides these, there are several rare types of eosinophilic dermatoses with unknown origin, in which eosinophil infiltration is a central component and affects specific tissue layers or adnexal structures of the skin, such as the dermis, subcutaneous fat, fascia, follicles, and cutaneous vessels. Some typical examples are eosinophilic cellulitis, granuloma faciale, eosinophilic pustular folliculitis, recurrent cutaneous eosinophilic vasculitis, and eosinophilic fasciitis. Although tissue eosinophilia is a common feature shared by these disorders, their clinical and pathological properties differ dramatically. Among these rare entities, eosinophilic pustular folliculitis may be associated with human immunodeficiency virus (HIV) infection or malignancies, and some other diseases, like eosinophilic fasciitis and eosinophilic cellulitis, may be associated with an underlying hematological disorder, while others

are considered idiopathic. However, for most of these rare eosinophilic dermatoses, the causes and the pathogenic mechanisms remain largely unknown, and systemic, high-quality clinical investigations are needed for advances in better strategies for clinical diagnosis and treatment. Here, we present a comprehensive review on the etiology, pathogenesis, clinical features, and management of these rare entities, with an emphasis on recent advances and current consensus.

Keywords Eosinophilic dermatoses · Eosinophilic cellulitis (Wells syndrome) · Granuloma faciale · Eosinophilic pustular folliculitis · Recurrent cutaneous eosinophilic vasculitis (RCEV) · Eosinophilic fasciitis (Shulman disease)

Introduction

Eosinophilia has been generally considered to be a hallmark of parasitic infestation and allergic diseases, especially asthma and atopic dermatitis. While the precise mechanisms of how eosinophils participate in the pathogenic process of these diseases remain mysterious, the conspicuous presence of eosinophils in a much broader spectrum of human disorders has been increasingly unveiled [1–3]. These include diseases associated with blood eosinophilia and/or tissue eosinophilia, in which eosinophilic infiltration may involve one or more organs such as skin, lungs, heart, gastrointestinal tract, and nervous system [3, 4]. Among these, a variety of skin diseases characterized by eosinophil infiltration and/or degranulation in skin lesions, with or without blood eosinophilia, is termed as eosinophilic dermatoses, or eosinophilic skin diseases [5].

The most common eosinophilic dermatoses lie in the allergy-related group, including allergic drug eruption, urticaria, allergic contact dermatitis, atopic dermatitis, and eczema, as well as prurigos. Other frequently seen disorders associated

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with skin eosinophilia include parasitic infestations, arthropod bites, urticarial vasculitis, and autoimmune blistering skin diseases such as dermatitis herpetiformis and bullous pemphigoid [1, 5].

Besides these well-characterized, common skin diseases, there are still several rare types of eosinophilic dermatoses with unknown origin. In each of these rare dermatoses, eosinophil infiltration affects specific tissue layers or adnexal structures of the skin, such as the dermis, subcutaneous fat, fascia, follicles and cutaneous vessels, and is considered to be a central component implicated in the pathogenic mechanisms [4]. Some typical examples are eosinophilic cellulitis, granuloma faciale, eosinophilic pustular folliculitis, recurrent cutaneous eosinophilic vasculitis, and eosinophilic fasciitis. However, these diseases are rare and mostly sporadic, and usually lack large-scale, systematic investigation. The purpose of this review is to present a comprehensive collection of both etiopathogenesis and clinical information for these rare entities, with an emphasis on recent advances and current consensus.

Eosinophil Biology and Its Roles in Eosinophilic Disorders

Complex mechanisms are involved in eosinophil infiltrating and its consequent pathogenic processes, and they may differ in various conditions or disorders. But there are some overarching mechanisms contributing to these processes (Fig. 1).

Cytotoxic and Proinflammatory Effects of Eosinophils

In the large granules of eosinophils, there are four highly toxic arginine-rich proteins tightly related to the function of these cells: the major basic protein (MBP), eosinophil peroxidase (EPO), the eosinophil protein X/eosinophil derived neurotoxin (EPX/EDN), and eosinophil cationic protein (ECP) [6]. These granule proteins are cationic toxins able to mediate damage to tissues [7]. When eosinophils become activated in response to a variety of stimuli, secretion of these granule contents into the tissue, also termed as degranulation, helps kill microbes, parasites, and even tumor cells [8], and participates in a wide range of inflammatory reactions, which may lead to tissue damage, fibrosis, and development of hypercoagulability [4, 9, 10]. Besides these cytotoxic granular proteins, other inflammatory mediators are also derived from eosinophils and play roles in the inflammatory processes, including various cytokines, chemokines, lipid mediators, and superoxide [4]. Additionally, recent advances have unveiled complex immunomodulatory functions of eosinophils, including its role as antigen-presenting cells (APCs) [11].

Migration and Chemotaxis of Eosinophils

Eosinophils aggregate at the inflammation sites in tissue in response to various inflammatory mediators or adhesion molecules through surface or cytoplasmic receptors. For instance, the migration of circulating eosinophils from blood vessels into the inflammatory tissue can be mediated by very late activation antigen-4 (VLA4), an alpha-4 integrin expressed on eosinophils, that binds to vascular cell adhesion molecule 1 (VCAM-1) on vascular endothelium (Fig. 1) [12]. Then eosinophils may migrate in the lesional sites in response to chemoattractants such as eotaxin-3 that binds to its receptor CCR3 on eosinophils (Fig. 1) [4]. Another chemoattractant named as regulated on activation, normal T cell expressed and secreted (RANTES), may also be implicated in this chemotactic process, although it has similar effect on monocytes, natural killer (NK) cells, basocytes, and T lymphocytes and is not specific to eosinophils [13].

Cytokines Related to Eosinophil Biology

In many diseases with eosinophilia, cytokines such as interleukin (IL)-5, IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF), play crucial roles in inducing the trafficking, survival, activation, and degranulation of eosinophils [4]. Especially, IL-5 has a dominating effect in regulating eosinophil differentiation and proliferation [4]. Cytokines produced by eosinophils themselves also include IL-5, IL-3, and GM-CSF, resulting in autocrine effects on eosinophil survival and function (Fig. 1) [14]. Based on these understandings, a humanized monoclonal antibody specifically targeting IL-5, known as mepolizumab, has been developed and used as a medication to deplete eosinophils in certain diseases, like asthma [7]. It can be inferred that this treatment modality may have the potential to be widely employed in the treatment of eosinophilia-associated diseases, including many eosinophilic dermatoses [7, 15].

Eosinophilic Skin Diseases: Pathogenic Mechanisms, Clinical Features, and Strategies of Diagnosis and Treatment

There are a wide variety of human disorders associated with eosinophilic infiltration, with or without eosinophil degranulation, in the skin lesions. A categorized list of these eosinophilic skin diseases is present in Table 1. Among these, allergy- or hypersensitivity-related disorders and parasitic infestations are most commonly seen and make up the majority of eosinophilic skin diseases. Meanwhile, some other eosinophilic dermatoses are rare and less well understood. Here, we selected five of these rare entities that are characterized by

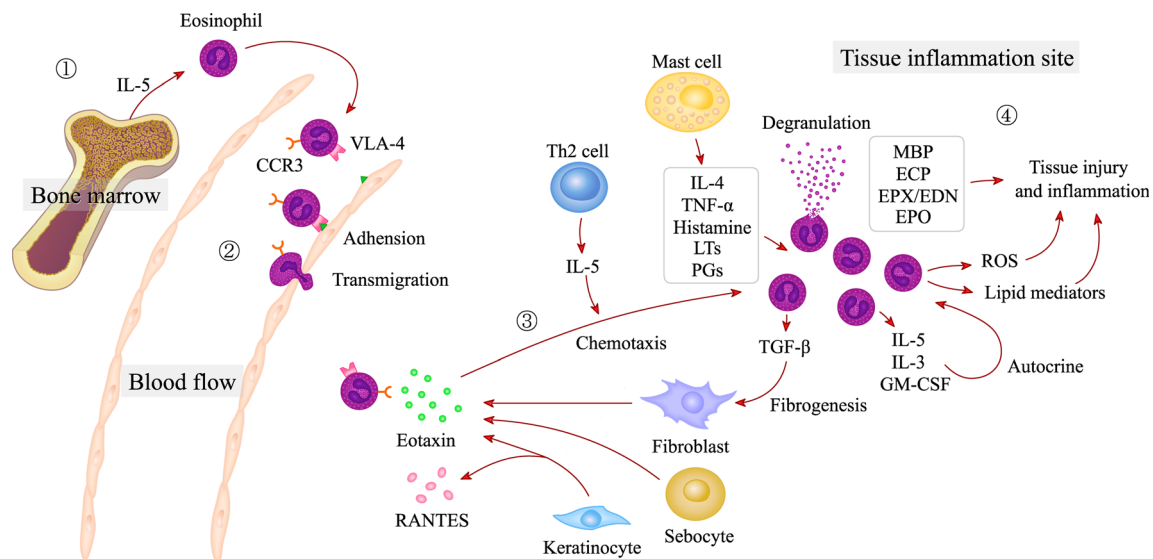


Fig. 1 An illustration of the mechanisms in which eosinophils transmigrate from blood flow into the tissue and participate in the pathogenic processes associated with tissue eosinophilia. *VLA-4* very late activation antigen-4; *CCR3* C-C chemokine receptor type 3; *RANTES* regulated on activation, normal T cell expressed and secreted;

LTs leukotrienes; *PGs* prostaglandins; *MBP* major basic protein; *EPO* eosinophil peroxidase; *EPX/EDN* eosinophil protein X/eosinophil-derived neurotoxin; *ECP* eosinophil cationic protein; *ROS* reactive oxygen species; *Lipid mediators* including leukotrienes, platelet-activating factor (PAF), prostaglandin E1/E2 and other mediators

eosinophilic infiltration in specific structures or appendices of the skin, and presented a comprehensive review of their etiology, pathogenesis, clinical features, strategies of diagnosis and treatment, and prognosis, with recent advances and current consensus emphasized.

Eosinophilic Cellulitis (Wells Syndrome)

Eosinophilic cellulitis, also known as Wells syndrome (WS), is first described by Wells in 1971 as a recurrent granulomatous dermatitis with eosinophils [16]. The term “eosinophilic cellulitis” was proposed by Wells and Smith in 1979 [17]. As a rare inflammatory dermatosis, it has fewer than 200 cases reported in the literature by 2012 [18].

Etiology

The etiology of WS is unclear. Among all the cases reported in the literatures, some appear to be idiopathic, while many others suggest a triggering event or be associated with an underlying disorder, which we discussed as follows:

- (1) Triggering factors include arthropod bites, viral or bacterial infections, drugs and vaccines. Bites or stings of arthropods such as mosquitoes [21], flea stings [19], honeybee stings [20], tick bites [19], spider bites [19], and centipede bites [21] are reported to have causal relationship with WS in some cases. It is inferred by in vitro experiments that mosquito salivary gland extracts injected intradermally by mosquito bites may serve as

antigens for T cells, possibly leading to the eosinophil-associated reaction [22]. Infection of viruses such as parvovirus B19 [23–25], herpes simplex virus (HSV)-2 [26], varicella zoster virus (VZV) [27], and mumps virus [17], and parasite infections including ascariasis [28] and *Toxocara canis* infection [29, 30] have also been suggested as causatively related to WS in some cases. Heelan et al. [31] reviewed the literatures and recorded 25 cases of drug-induced WS [31]. Among these cases, drugs reported to be a causative factor include antibiotics [32–36], anticholinergic agents [36], anaesthetics [33, 36], nonsteroidal anti-inflammatory drugs (NSAIDs) [33, 35, 36], thyroid medications [34, 36], chemotherapeutic agents [32, 37], thiazide diuretics [31], thiomersal containing vaccinations [38–40], and anti-tumor necrosis factor (TNF) agents [41–43].

- (2) Cases associated with an underlying disorder. These underlying disorders include hematological malignancies such as chronic myeloid leukemia [44], chronic lymphocytic leukemia [44, 45], and non-Hodgkin's lymphocytic lymphoma [46], as well as nonhematological malignancies such as renal cell carcinoma [47], colon carcinoma [48], and nasopharyngeal carcinoma [48]. It has also been reported that WS is associated with Churg–Strauss syndrome, a rare autoimmune granulomatous vasculitis, in some cases [49–53]. Sakaria et al. [54] reported a case of WS associated with ulcerative colitis, which resolved upon effective treatment targeting ulcerative colitis. There have also been reports that WS may occur in association with hypereosinophilic syndrome, supporting the hypothesis that these two conditions belong to the same nosological spectrum [55, 56].

Table 1 A categorized list of eosinophilic dermatoses including systemic diseases with cutaneous eosinophilia

Categories	Diseases	Clinical and/or pathological features
Allergy or hypersensitivity	Allergic drug eruption	An adverse drug reaction presenting as skin lesions, usually itchy, which could be categorized into various types according to the clinical manifestations
	Urticaria	Transient onset of pruritic wheals, sometimes with angioedema; an individual wheal usually disappears spontaneously within 24 h
	Allergic contact dermatitis	A well-circumscribed, localized eruption with itchy and (or) burning sensation caused by direct skin contact with a foreign allergen
	Atopic dermatitis	Dry skin, itchy eczematous lesions primarily located on the face, neck and flexor sides of limbs; starts in childhood; a history of family or personal atopic diseases; increased serum IgE
Parasitosis	Nummular eczema	Isolated, itchy, eczematous plaques in rounded shapes; located primarily on limbs, as well as on the trunk, face and neck
	Papular urticaria	Chronic or recurrent individual papules on the basis of wheals, often with a central punctum; caused by arthropod bites
	Scabies	An itchy, contagious skin infection caused by the mite <i>Sarcoptes scabiei</i>
	Seabather's eruption (SBE)	An intensely itchy dermatitis characterized by small red papules that occurs predominantly in regions of the body covered by bathing costumes, after exposure to marine water; caused by a hypersensitivity reaction to larval-stage thimble jellyfish (<i>Linuche unguiculata</i>) or sea anemone (<i>Edwardsiella lineata</i>)
Fungal infection	Cercarial dermatitis	Also known as "swimmer's itch"; a commonly seen water-borne disease caused by skin infection by infective larvae (cercariae) of schistosomatid flukes; presenting as itchy maculopapular skin eruptions occurring within hours of exposure to cercariae-affected freshwater
	Other helminth infections	E.g., strongyloidiasis, filariasis, toxocariasis
	Cutaneous coccidioidomycosis	Solitary granulomatous plaques or multiple papular, nodular, or pustular lesions with tissue eosinophilia
	Lymphoma	Hodgkin lymphoma, or cutaneous T cell lymphoma (CTCL), especially mycosis fungoides (MF)
Neoplasms or hyperplastic disorders	Eosinophilic granuloma	A most frequently reported and least severe variant of Langerhans cell histiocytosis (LCH), which is histologically characterized by the proliferation of Langerhans cells; usually presenting as a chronic, localized lesion in bone or lung, most commonly affecting children
	Cutaneous mastocytosis (CM)	The most frequent form of mastocytosis, a rare disease characterized by an abnormal accumulation and proliferation of mastocytes in one or more organs; mostly occurs in infancy or childhood, but sometimes occurs in adulthood; skin lesions vary in presentation, with urticaria pigmentosa (UP) as the most frequent form (Fig. 2)
	Eosinophilic dermatosis of hematologic malignancy	A pruritic, papular and occasionally vesicular eruption with an eosinophil-rich infiltrate histopathologically, associated with a hematologic malignancy such as chronic lymphocytic leukemia, acute monocytic leukemia, acute lymphoblastic leukemia, mantle cell lymphoma, large cell lymphoma, and myelofibrosis
	Cutaneous pseudolymphoma	A heterogeneous group of benign reactive T- or B-cell lymphoproliferative processes of diverse causes including arthropod bites, trauma, drugs and vaccines; clinical presentations featured by lymphomatous-appearing patches and plaques (Fig. 3)
HIV-associated eruptions	Pruritic papular eruption (PPE) of HIV	Chronic, sterile pruritic papules and pustules on the extensor surfaces of the arms, dorsa of the hands, trunk, and face with sparing of the palms and soles; mostly in the advanced immunosuppressive stage; skin biopsy showing spongiosis, parakeratosis with perivascular mononuclear cell infiltration, sometimes with eosinophilic infiltrate
	Eosinophilic pustular folliculitis	(Introduced in the main text)
Cutaneous vasculitis	Urticarial vasculitis	Recurrent episodes of urticarial lesions; persistent greater than 24 h; residual hyperpigmentation following resolution; histology showing leukocytoclastic vasculitis (Fig. 4)
	Recurrent cutaneous eosinophilic vasculitis (RCEV)	(Introduced in the main text)
Autoimmune blistering skin diseases	Dermatitis herpetiformis	An autoimmune, pleiomorphic, papulovesicular disorder associated with celiac disease and gluten sensitivity; intensely pruritic; characterized by subepidermal bullae and granular IgA deposits in the dermal papillae (Fig. 5)

Table 1 (continued)

Categories	Diseases	Clinical and/or pathological features
Systemic diseases	Pemphigus herpetiformis	A clinical variant of pemphigus that resembles the clinical manifestations of dermatitis herpetiformis and presents with the immunopathologic features of pemphigus, characterized by intraepidermal blister with eosinophilic spongiosis and IgG deposits on keratinocyte cell surface
	Bullous pemphigoid	A common autoimmune subepidermal bullous disease affecting elderly patients and, sometimes, children; characterized by subepidermal blisters, inflammatory infiltrate with an eosinophil predominance, and IgG and complement C3 deposits in a linear band at the dermal-epidermal junction
	Eosinophilic granulomatosis with polyangiitis (EGPA)	Formerly named as Churg–Strauss syndrome (CSS); a rare systemic vasculitis characterized by necrotizing vasculitis with eosinophilic infiltration of small- and medium-sized vessels, mainly affecting middle-aged individuals; associated with asthma and marked blood eosinophilia; severity varies from patient to patient, and some cases could be life-threatening
	IgG4-related disease	Nonspecific indurated skin papules, plaques and nodules only reported in Asian; multiple organs affected; skin biopsy showing a dense, mixed-cell dermal infiltration containing lymphocytes, plasma cells and eosinophils along with fibrosis; immunohistochemical stains positive for IgG4
	Hypereosinophilic syndrome (HES)	A heterogeneous group of rare disorders characterized by persistent peripheral hypereosinophilia associated with multiple organ involvement and dysfunction, often including the skin
Pediatric diseases	Annular erythema of infancy	Nonpruritic, figurate erythema with annular, oval circinate, or polycyclic patterns, without general complaints, onset in the first year of life; skin biopsy showing a perivascular and interstitial lymphocytic infiltrate with numerous eosinophils; without blood eosinophilia
	Erythema toxicum neonatorum (ETN)	Transient erythema, wheals, papules, or pustules, commonly occurring within the first 48 h of life and resolving spontaneously without sequelae over the course of a week; skin biopsy showing an abundance of eosinophils
	Juvenile xanthogranuloma (JXG)	A rare histiocytic disorder that typically affects children, or adults of all ages; single or, rarely, multiple yellow and brown nodules, several millimeters in diameter, usually on the face and neck; occasionally with internal organ involvement
Pregnancy- related disease	Incontinentia pigmenti (Bloch-Sulzberger syndrome)	A rare X-linked multisystem disorder with skin, eye, central nervous system and tooth abnormalities, caused by a mutation of IKBKG; (the first stage) red papules and vesicles grouped on an erythematous base and scattered in swirls, and patches along Blaschko's lines, occurring in the first few weeks after birth; histology showing spongiotic vesicles containing eosinophils; (the second stage) thickened warty-appearing plaques with eosinophils in epidermis and dermis (Fig. 6)
	Pruritic urticarial papules and plaques of pregnancy (PUPPP)	Pruritic, erythematous, urticarial papules and plaques mostly on the abdomen and proximal thighs, usually appearing in the third trimester of pregnancy and regressing within 6 weeks postpartum (Fig. 7)
	Pemphigoid gestationis	Diffuse, pruritic subepidermal bullous eruptions that begin periumbilically and spread to involve the rest of the body, during pregnancy and postpartum; linear deposition of complement C3 along the basement membrane zone
	Eosinophilic cellulitis (Wells syndrome)	(Introduced in the main text)
Ungrouped diseases	Granuloma faciale	(Introduced in the main text)
	Eosinophilic fasciitis (Shulman disease)	(Introduced in the main text)
	Ofuji's papulopythoderma	Pruritic erythematous papules and extensive erythema sparing all skin folds (deck-chair sign), mostly in elderly patients; peripheral eosinophilia, lymphocytopenia and increased serum IgE; frequently associated with cutaneous T cell lymphoma (CTCL) or visceral malignancy
	Episodic angioedema with eosinophilia (Gleich's syndrome)	Recurrent angioedema, itchy urticaria, rapid weight gain, elevated IgM levels, marked blood eosinophilia, and eosinophil infiltrates in the dermis

Table 1 (continued)

Categories	Diseases	Clinical and/or pathological features
	Eosinophilic lymphfolliculosis of the skin (Kimura's disease)	Deep subcutaneous masses primarily involving the head and neck region, often with regional lymphadenopathy and salivary gland involvement; mainly reported in Asian; skin biopsy showing lymphoid proliferation with eosinophilic infiltration; marked blood eosinophilia and elevated serum IgE level
	Epithelioid hemangioma	Also known as angiolymphoid hyperplasia with eosinophilia (ALHE); solitary or multiple, 0.5–3 cm, red to brown firm papules and nodules, occurring in the head and neck region with a predilection for the peri-auricular area; usually occurring during the early and mid-adult life (Fig. 8)
	Eosinophilic ulcer of the oral mucosa (EUOM)	A rare, benign disorder also known as traumatic ulcerative granuloma with stromal eosinophilia (TUGSE), or Riga–Fede disease (a term mainly used in infant patients); a solitary ulcer of the oral mucosa, with an elevated, indurated border and a yellowish fibrinous base, usually affecting the tongue, in either adults or infants; with a chronic and self-limiting course; histopathology featured by a diffuse inflammatory infiltrate rich in eosinophils

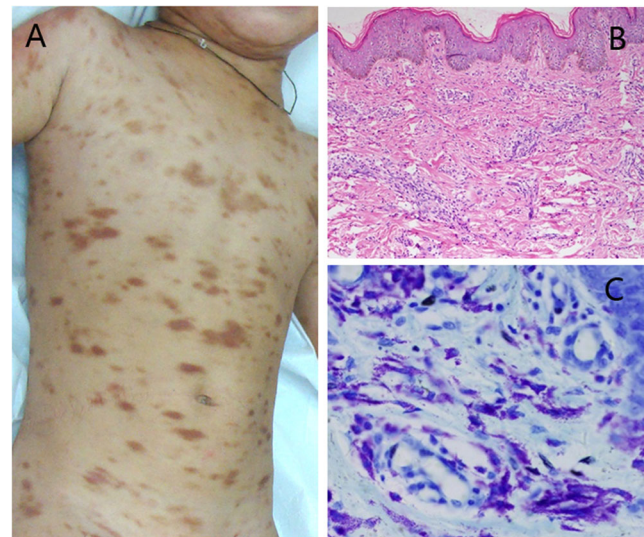


Fig. 2 Urticaria pigmentosa. **a** Brown macules and maculopapules scattered on the trunk and the limbs, with a positive Darier's sign, which appeared shortly after birth and kept recurring during the past 2 years in a 2-year-old girl. **b** Plentiful infiltrate of mast cells in the dermal papilla layer and reticular layer (hematoxylin–eosin, original magnification $\times 100$). **c** Perivascular infiltrate of spindle-shaped mast cells with metachromatic granules in the cytoplasm (toluidine blue staining, original magnification $\times 400$)

Pathogenesis

The pathogenesis of WS remains largely unknown. Although it is still debated whether WS constitutes a disease entity, a nonspecific hypersensitivity reaction in response to exogenous and (or) endogenous stimuli is generally considered as its important mechanisms [57]. Dysregulated tissue eosinophilia plays important roles in the pathogenic process. Circulating CD4+CD7–T cells may be implicated by producing IL-5 [58], and IL-5 overproduction may participate in eosinophil accumulation [59]. IL-2 enhances platelet-activating factor-stimulated release of eosinophil cationic protein from CD25-expressing, but not from CD25-negative eosinophils, and therefore, CD25-expressing eosinophils are related to higher risk of eosinophil degranulation, and subsequent tissue damage, mediated by IL-2 [60].

Clinical Manifestation

WS affects people of all races without a significant sex predilection. It is reported mostly in adults, but also in pediatric population [61]. It typically appears as a sudden-onset of multiple or single, large, well-circumscribed, edematous erythema that may have annular configuration (Fig. 9a) and are usually pruritic and/or painful. These erythema generally develop into indurated erythematous plaques that may last weeks or years and tend to have recurrent episodes without scarring [17, 34, 36]. Patients tend to report itching and burning that precedes the onset of these skin lesions [62]. The limbs and the

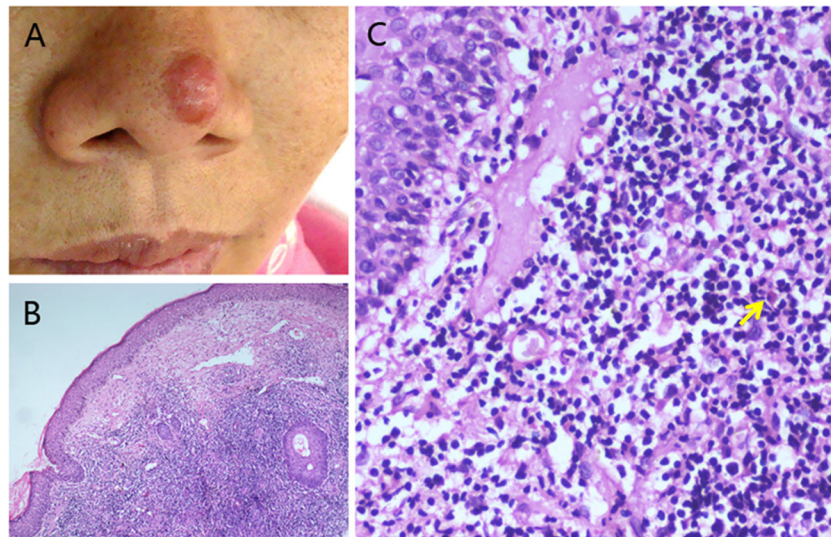


Fig. 3 Cutaneous pseudolymphoma. **a** A well-circumscribed, soybean-sized, hemispheric, erythematous nodule on the tip of the nose in a 40-year-old woman. **b** Dense perivascular and periadnexal inflammatory infiltrate in the dermis, mainly of lymphocytes and histiocytes (hematoxylin–eosin, original magnification $\times 100$). **c** Dense dermal

infiltrate of lymphocytes, with inconspicuous dysplasia, and histiocytes, few neutrophils and eosinophils (hematoxylin–eosin, original magnification $\times 400$; arrow an eosinophil). Immunohistochemistry results (no photo provided here) showed CD45RO (++) , CD20 (++) , and CD30 (–)

extremities are the sites of predilection, although skin lesions presenting on the trunk, on the scalp or on the face have also been reported [18]. The clinical appearance of WS often resembles other dermatoses such as urticaria, cellulitis, and contact dermatitis [63]. Systemic symptoms such as arthralgia and fever may occur in some cases [17, 36]. Transient hypereosinophilia is common [17, 36, 64, 65]. Atypical clinical presentations of WS include bullous, nodular, or papulonodular skin lesions, although rare [31]. For example, bullous skin lesions have been reported in both idiopathic cases [66] and in cases with underlying disorders such as non-Hodgkin's lymphoma [46] and Churg–Strauss syndrome [53].

Some WS patients have an associated underlying disorder such as carcinomas and hematological malignancies. Hypereosinophilic syndrome [55], eosinophilic annular erythema [67, 68], and Churg–Strauss syndrome [49, 51, 52] may

also occur in association with WS in some patients. Eosinophilic annular erythema (EAE), characterized by recurrent appearance of persistent nonpruritic, urticarial annular lesions, is a rare benign disorder originally described in children [68]. Although it is histologically distinct from WS, EAE has recently been proposed to be a clinical variant in the spectrum of WS, which is characterized by chronic course with high relapse rate and recalcitrance to typical treatment [67, 69].

Churg–Strauss syndrome, characterized by peripheral eosinophilia and infiltration of eosinophils into systemic organs, has also been reported to be coincidentally overlapped with WS in a few cases [53, 70, 71]. Ratzinger et al. [70] proposed that these two diseases might be different stages in a same pathogenic process, and it could be worthwhile to evaluate and follow WS patients for the possibility of Churg–Strauss syndrome.

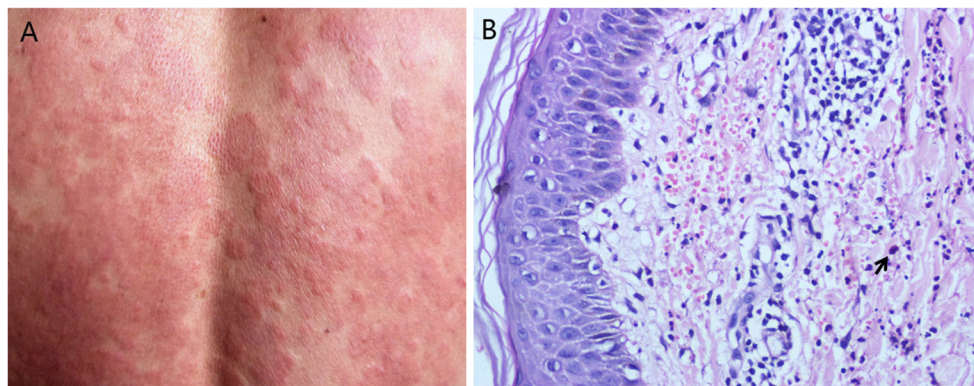


Fig. 4 Urticarial vasculitis. **a** Widespread, painful, hive-like red plaques on the trunk and the limbs in a 46-year-old man, with recurrent episodes for 3 years. Serum tests showed hypocomplementemia. **b** Swelling of dermal

vascular endothelial cells with extravascular red blood cells and perivascular infiltrate of lymphocytes, neutrophils, nuclear dusts, and few eosinophils (hematoxylin–eosin, original magnification $\times 400$; arrow: an eosinophil)

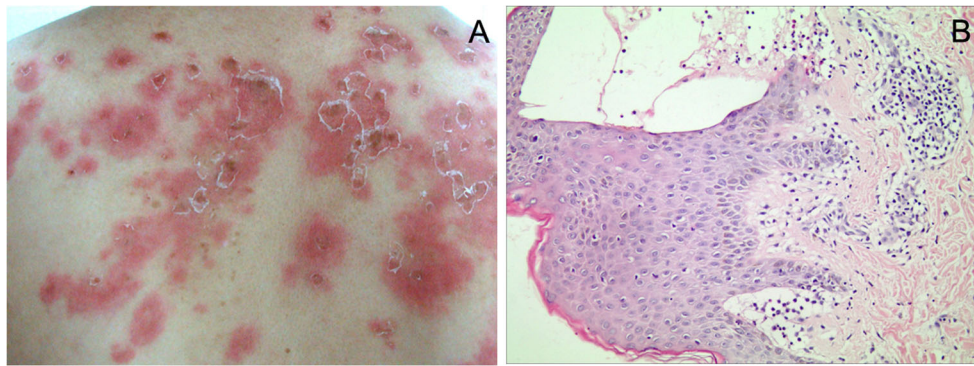


Fig. 5 Dermatitis herpetiformis. **a** Intensely pruritic, red macules or patches with vesicles and annular scales on their surface in a 23-year-old woman, with recurrent episodes associated with gluten-containing food intake, for one year. **b** Subepidermal vesicles and papillary

microabscess with neutrophil and eosinophil infiltration, and perivascular infiltrate of lymphocytes and few neutrophils and eosinophils in the upper dermis (hematoxylin–eosin, original magnification $\times 200$)

Histopathology

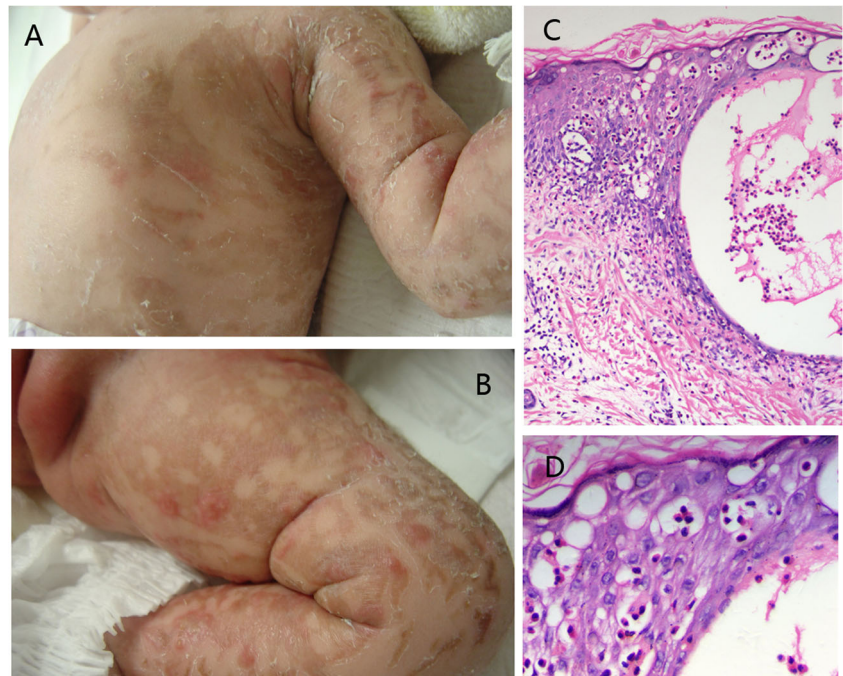
Typically, the histopathological features of WS are characterized by dermal edema, marked dermal eosinophilic infiltrates, and flame figures in which degranulated eosinophilic material adheres to collagen [17, 32, 34] (Fig. 9b–d). Vasculitis is usually absent in WS [18]. The histological findings vary depending on the time when the biopsy is taken [72]. At an early phase of WS, the histopathological changes are featured by dermal edema and massive dermal infiltration of granulocytes, predominantly eosinophils. A subacute phase is characterized by dermal infiltrates of phagocytic histiocytes and the formation of flame figures. In an older phase, or the resolution stage, the infiltration of eosinophils gradually reduces, leaving histiocytes and giant cells surrounding the remaining flame figures.

Flame figures, although distinctive, are not pathognomic of WS [73]. Flame figures may also be observed in other diseases such as pemphigoid and its variants, Churg–Strauss syndrome, herpes gestationis, eczema, severe prurigo, drug eruption, and follicular mucinoses [73–75], as well as parasitosis and spider [18, 19]. Thus, an integration evaluation of both clinical and histopathological findings is necessary for the diagnosis.

Diagnosis and Differential Diagnosis

The diagnosis of WS should be based on a comprehensive evaluation of the history, clinical manifestations, and histopathological findings, and exclusion of other possible causes [31, 76]. Typically, recurrence of erythematous

Fig. 6 Incontinentia pigmenti. **a–b** Red papules and papulovesicles scattered on the background of brown or hyperpigmented patches that are arranged in a reticular pattern and along Blaschko's lines in a 19-day-old female infant, who had an onset of the disease after birth. **c** Epidermal spongiosis and intraepidermal vesicles with massive infiltrate of eosinophils, and perivascular infiltrate of lymphocytes and eosinophils in the upper dermis (hematoxylin–eosin, original magnification $\times 100$ and $\times 400$, respectively)



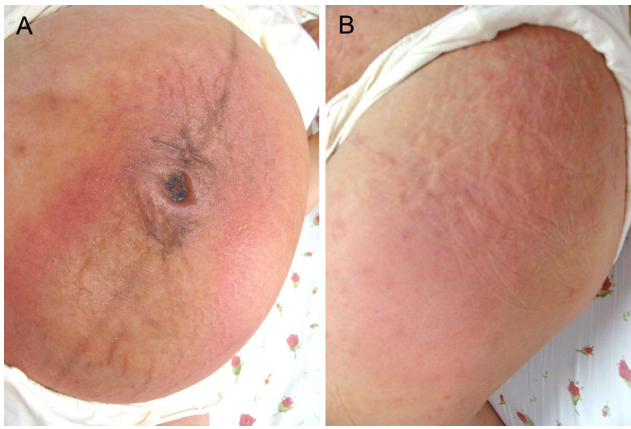


Fig. 7 Pruritic urticarial papules and plaques of pregnancy (PUPPP). Widespread, intensely pruritic, erythematous papules, papulovesicles, and wheals on the abdomen (a) and the legs (b), especially along the stretch marks, in a 34-year-old pregnant woman who was in the 33rd gestational week with a set of quadruplets

cutaneous lesions resembling cellulitis without clear source of infection, and irresponsiveness to antibiotic therapy should lead to a consideration of WS. In a proposed diagnostic criteria for WS by Heelan et al. [31], any of the following variants of skin lesions with a relapsing-remitting course could be considered possible appearances of WS: plaque type, annular granuloma-like, urticaria-like, papulovesicular, bullous, papulonodular, and fixed drug eruption-like. The diagnosis of WS can also be supported by blood eosinophils and histopathological findings including dermal edema, eosinophilic dermal infiltration, and flame figures.

The differential diagnosis is broad and usually includes bacterial cellulitis, erysipelas, urticaria, contact dermatitis, allergic drug eruptions, and some less common diseases such as erythema chronicum migrans, granuloma annulare [63, 65]. Churg–Strauss syndrome and hypereosinophilic syndrome should not be neglected [56, 70]. It is also important to keep aware that WS may occasionally be associated with an underlying malignancy so that we do not miss the important diagnosis.

Treatment

As a first-line therapy, systemic corticosteroids are the most effective treatment for WS [18, 62]. Oral prednisone at 20–30 mg/day usually achieves good therapeutic response, and leads to the clearance of skin lesions within several weeks. For cases with persistent and frequently recurrent scenario, low-dose (5 mg) alternate-day prednisone can be a potentially effective maintenance, as suggested by Coldiron et al. [77].

However, some patients with WS are resistant to corticosteroids or are intolerant to the adverse effects of long-term use [18]. For these cases, treatment may need to be combined with or replaced by other medications. These alternative therapeutic agents, as reported, include dapsone [78], tacrolimus [79], and cyclosporine [80]. However, the effectiveness of all these alternative therapies are based on sporadic case reports and individual experience.

There was a recent report of WS successfully treated with adalimumab, a tumor necrosis factor (TNF)- α inhibitor [81]. It was unclear how adalimumab managed to inhibit the pathogenesis of eosinophilic cellulitis in this reported case, though recent evidence in murine models suggests that the TNF pathway may play a role in antigen-specific immunoglobulin E (IgE) production and eosinophil recruitment [82, 83]. Also interesting is that WS has been reported to be triggered by TNF- α inhibitors, including adalimumab and etanercept in some cases [41, 43]. Thus, it remains to be elucidated whether TNF- α inhibitors can be used as a treatment for recalcitrant WS.

Treating the underlying condition or triggering factor can also be beneficial for the resolution of WS [26, 54, 62]. Antihistamines can help relieve the pruritus [66]. However, antibiotics hold no therapeutic effect for WS [84].

Local therapies can be used in combination with systemic therapy, and preferentially in cases of limited disease or for clearance of residual lesions [18]. Corticosteroids, both topical

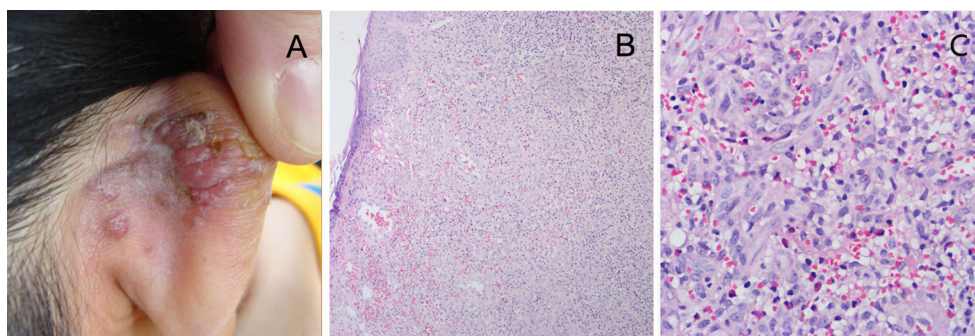
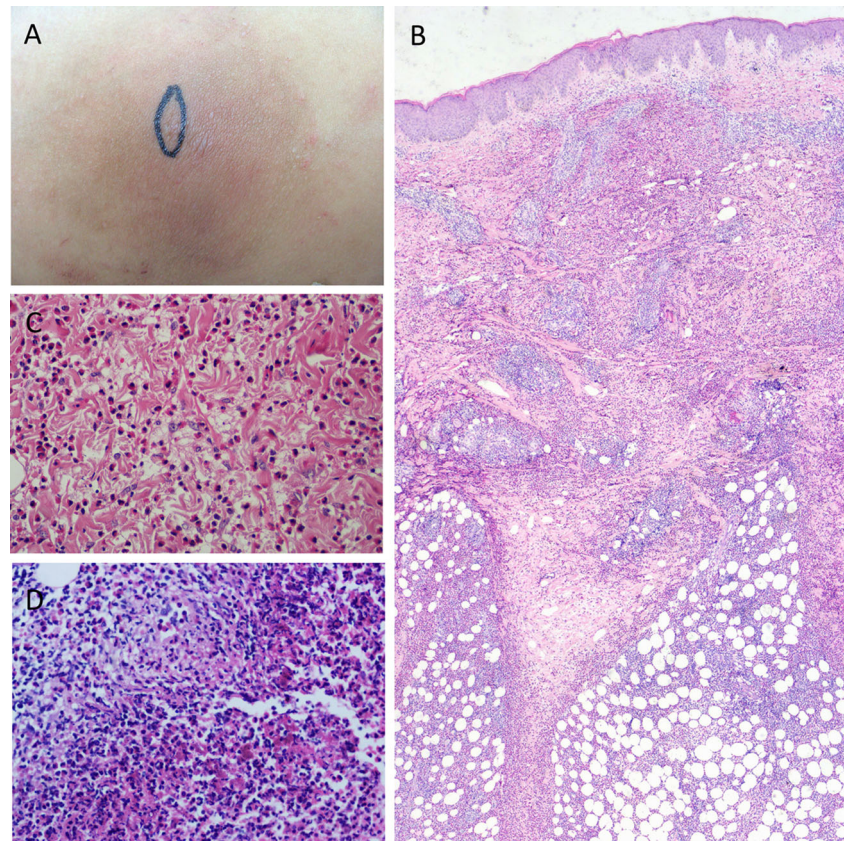


Fig. 8 Epithelioid hemangioma. a Pruritic, erythematous papules and nodules with crusts on the dorsal side of the right auricle, lasting for over 6 months, in a 45-year-old woman. b–c Swollen endothelial cells with epithelioid appearance, and hyperplasia of vascular and lymph

tissues with eosinophil infiltration in the dermis (hematoxylin–eosin, original magnification $\times 100$ and $\times 400$, respectively). Immunohistochemistry results (no photo provided here) showed Vim (++), CD31 (+), CD34 (+), F8 (+), SMA (+), and EMA (–)

Fig. 9 Eosinophilic cellulitis. **a** A painful, edematous, and brown-red 3×3 cm plaque on the right waist in an 11-year-old girl for 10 days, with a stiff and tender 2.8×2.8 cm nodule inside on palpation. **b–c** Histopathology showed diffuse infiltrate of eosinophils and histiocytes around vessels and between collagen fibers in the dermis and the subcutaneous fat tissue (hematoxylin–eosin, original magnification ×100 and ×400, respectively). **d** Flame figures in the dermis (hematoxylin–eosin, original magnification ×400)



application [18] and intralesional injection [85], may be effective. Topical tacrolimus, used in combination with antihistamine drugs, has also been reported to be effective in at least one reported case [66].

Prognosis

WS tends to run a benign course [61, 62, 86]. Most patients recover without difficulty, although recurrences may occur. The skin lesions take weeks to months to resolve, typically resulting in morphea-like residual skin atrophy and hyperpigmentation, without scarring [17]. A noteworthy fact is the possible overlap of WS with an underlying disease, which might contribute to a different prognosis [18]. Thus, a comprehensive evaluation and follow-up for the possible associated diseases, such as hematologic malignancies, Churg–Strauss syndrome and hypereosinophilic syndrome, are necessary for these patients.

Granuloma Faciale

Granuloma faciale (GF) is an uncommon, benign, chronic inflammatory skin disease of unknown origin [87, 88], which was first defined in 1950s [89–91]. It usually manifests as a solitary reddish-violaceous plaque on the face, whereas

extrafacial involvements can also occur. GF tends to be resistant to a variety of therapies including corticosteroids.

Etiology and Pathogenesis

The etiology of granuloma faciale remains unknown [87]. Actinic exposure might be a possible predisposing factor, as the predilection sites of GF are the facial area, and the skin lesions may exacerbate with sunlight exposure [88, 92]. Other hypotheses propose that it might be a form of vasculitis mediated by a localized persistent immune complex disease, or an Arthus-like reaction [93].

An interesting observation in skin biopsies of GF is that the infiltration of eosinophils is in parallel with infiltration of CD4+ T cells [94]. Further evidence has suggested possible roles of clonally expanded skin-specific CD4+ cells and local overproduction of IL-5, as well as eosinophil activation in the lesion [95], in the pathogenic mechanisms [94]. Dendritic cells (DCs) can modulate helper T cell functions such as cytokine production, and its interaction with helper T cells is inferred to participate in the formation of GF lesions [96]. Other investigations have proposed the possible roles of a gamma-interferon-mediated process [97], and a classical pathway activation of complement [98], in the pathogenesis of this disorder.

Clinical Manifestation

GF mostly affects middle-aged men, typically in Caucasians [92, 93]. A featured presentation is a solitary, reddish brown or violaceous, well-demarcated plaque on the face with a chronic, long-lasting course (Fig. 10a). The skin lesions could also appear as papules or nodules, which might coalesce into plaques, and could be either solitary or multiple [92, 93]. Their size varies from several millimeters to several centimeters in diameter. The lesions are usually smooth on the surface, with no tendency to ulcerate, but can often present with superficial telangiectasia [99] and prominent follicular orifices, sometimes showing a “peau d’orange” appearance [87]. Skin lesions of GF are generally asymptomatic, although burning or itching sensation may be present occasionally [92, 100]. The face, including the nose, cheeks, forehead, and preauricular areas is the predilection site in most patients with GF [92, 99]. Extrafacial skin lesions have rarely been reported, involving the scalp, trunk, arms, or thighs [99, 101–103].

GF is not considered to be associated with underlying systemic disease [87]. Nevertheless, a peculiar disorder, angiocentric eosinophilic fibrosis (EAF), may accompany granuloma faciale in rare cases [104, 105]. EAF is a rare, benign, fibrosing condition which mainly involves the sinonasal tract and the upper respiratory tract [106]. It shares many histologic characteristics with GF [107] and is regarded by some authors as a mucosal counterpart of GF [105, 108].

Laboratory examinations generally show unremarkable results in patients with GF, with the exception of occasional mild blood eosinophilia [93].

Histopathology

The histopathological findings of GF are diagnostic [88, 108]. An important feature is the presence of a Grenz zone of uninvolved dermis, located beneath the normal epidermis [88, 92,

93] (Fig. 10b). Below the Grenz zone is the dense dermal infiltrates of mixed inflammatory cells, mainly including neutrophils, eosinophils, and lymphocytes (Fig. 10c). The adnexal structures of the skin are usually spared [109].

Slight difference in histopathological changes may present depending on the developmental stage of the lesions. In the early stage, small-vessel vasculitis are commonly seen, showing perivascular inflammation with scant nuclear dust and damage in the vessel walls [108]. Few extravasated erythrocytes and hemosiderin deposition is present, which may contribute to the color of the lesions [108, 109]. In mature lesions, a dense infiltration of neutrophils, eosinophils, lymphocytes, and histiocytes become more prominent [88]. In old lesions, tissue fibrosis accompanying capillary proliferation can be observed [92, 93].

Diagnosis and Differential Diagnosis

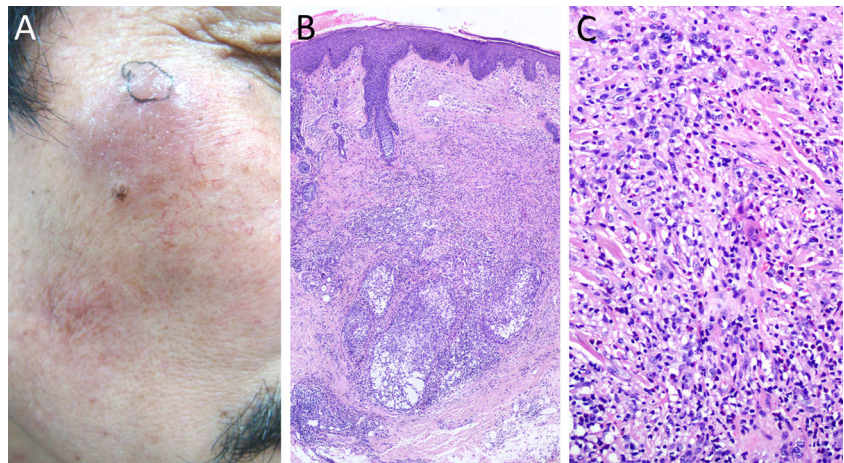
Diagnosis of GF is generally based on clinical features and histopathology [87, 88]. Skin biopsy is almost mandatory for the diagnosis, and of great value to rule out the main clinical differential diagnoses including erythema elevatum diutinum, sarcoidosis, discoid lupus, cutaneous lymphoid hyperplasia, cutaneous lymphomas, basal cell carcinoma, fungal, and mycobacterial infections (e.g., lupus vulgaris) [88, 92, 93, 110].

Recently, dermoscopy, as an adjuvant diagnostic tool, has shown beneficial values in assisting the diagnosis and differential diagnosis. Typically, dilated follicular openings are much more evident under dermoscopy, which enhance the differentiation of GF from its clinical simulators [87, 109, 111].

Treatment

GF is notoriously resistant to treatment [88]. Therefore, a variety of different treatment modalities have been tried, but none has proved to be consistently effective [88, 100]. These

Fig. 10 Granuloma faciale. **a** An asymptomatic, crusted, erythematous 1.7×2.0 cm plaque and irregular telangiectasis on the right malar area for 2 months in a 60-year-old man. **b–c** Dense dermal infiltrate of lymphocytes, histiocytes, and eosinophils, with the presence of a Grenz zone beneath the epidermis (hematoxylin–eosin, original magnification ×100 and ×400, respectively)



therapeutic options include dapsone, clofazimine, antimalarials, isoniazid, topical use or intralesional injections of corticosteroids, intralesional gold injections, topical psoralen ultraviolet A radiation (PUVA), dermabrasion, laser therapy, and more destructive treatments such as surgical excision and cryotherapy [88, 99, 100, 112]. Pulsed dye laser treatment often shows marked cosmetic improvement without scarring and is a recommended first-line treatment option [113–115]. More recently, topical tacrolimus treatment has been reported to be successful in quite a few patients with GF, and thus suggested to be a promising treatment option that is safe and effective [100, 109, 116].

Prognosis

GF is a benign inflammatory skin disease without systemic involvement [88]. However, the skin lesion is chronic and extremely long-lasting, and rarely resolves spontaneously [100, 109]. It is usually resistant to treatment, and tends to relapse after treatment [88, 92].

Eosinophilic Pustular Folliculitis

Eosinophilic pustular folliculitis (EPF), also known as eosinophilic folliculitis, is a rare, noninfectious inflammatory dermatosis characterized by recurrent episodes of pruritic follicular papules and pustules, and histopathologically associated with folliculotropic infiltration of eosinophils [117, 118]. This disease was first described by Ofuji et al. [119] in 1970. Since then, more than 300 cases of EPF have been reported in the English literature [118]. EPF is an important entity because in some patients it is associated with human immunodeficiency virus (HIV) infection, or a malignancy.

Etiology

The etiology of EPF remains unclear, although various conditions have been reported to be a possible related or causal factor in some patients [120, 121]. A frequently discussed factor is the association with HIV infection, hematologic malignancy, or other malignancies in some EPF cases, which are referred to as the immunosuppression-associated type of EPF [122–124]. It is generally considered that the immunocompromised status in these patients is causally related to the development of EPF. However, for this subgroup of patients, some intriguing issues have also been documented. First of all, some of the HIV-infected patients experience onset of EPF eruptions shortly after starting highly active anti-retroviral therapy (HAART), which invokes an argument that EPF may occur as a consequence of immune reconstruction syndrome rather than immunodeficiency in these HAART-treated cases [122, 125]. Second, among the EPF patients with hematologic

malignancy, such as lymphoma [126, 127] and leukemia [128], onset of EPF may occur after a bone marrow or stem cell transplantation, even though the transplantation has led to a successful remission of the hematological malignancy.

The classic EPF and the infantile type of EPF occur seldom with an obvious causal factor. Few of these patients have been reported to be possibly associated with parasitic infection, such as scabies [129], cutaneous larva migrans [129], and *Giardia intestinalis* infection [57]. Other possible related factors reported in sporadic cases include atopy [130] (e.g., a history of allergic rhinitis and asthma [131]), drugs [132] (e.g., chemotherapy [133], allopurinol [134], carbamazepine [135]), pregnancy [136, 137], and hepatitis C virus (HCV) infection [138].

Pathogenesis

The precise pathogenesis of EPF remains largely unknown. In EPF skin lesions, expression of intercellular adhesion molecule 1 (ICAM-1) by keratinocytes is identified on follicular epithelium, but not on epidermis, and expression of vascular cell adhesion molecule 1 (VCAM-1) by vascular endothelium is more often observed around hair follicles [139]. Expression of lymphocyte function-associated antigen 1 (LFA-1), which modulates the migration of eosinophils and lymphocytes, is also limited to follicular epithelium [139]. It is possible that these molecules are implicated in the selective migration of eosinophils and lymphocytes to the hair follicles in EPF.

Recent findings have suggested a pivotal role of prostaglandin D₂ (PGD₂) in the mechanisms of eosinophil infiltration and activation in the pilosebaceous units of EPF skin lesions. These studies may have been inspired by the fact that EPF has good therapeutic response to indomethacin, an NSAID drug, which is not only a cyclo-oxygenase (COX) inhibitor but also a potent agonist of chemoattractant receptor-homologous molecule expressed on T-helper type 2 cells (CRTH2), a PGD₂ receptor that generally expressed on eosinophils and other leukocytes including basophils [140].

Initially, it has been documented that the infiltrating inflammatory cells in EPF lesions express both hematopoietic PGD synthase (H-PGDS) [140, 141] and lipocalin PGD synthase (L-PGDS) [142], the two essential enzymes for generating PGD₂. As a consequence, two hypothetical mechanisms for eosinophil chemotaxis and activation by PGD₂ in EPF skin lesions are proposed. One possible mechanism involves the PGD₂-CRTH2 interaction [140, 142]. Briefly, eosinophils may accumulate in the skin lesions, where PGD₂ is produced, as a result of their chemokinetic and chemotactic responses to PGD₂ via CRTH2 receptors expressed on eosinophils. The other speculated mechanism is related to the role of PGD₂ in inducing sebocytes to overproduce eotaxin-3 via its interaction with peroxisome proliferator-activated receptor gamma (PPAR γ), a molecule expressed on sebocytes [141].

Eotaxin-3 subsequently plays its role as a chemoattractant to eosinophils, which express the eotaxin-3 receptor CCR3 [141].

Immunohistochemical staining techniques have also detected significant infiltration of basophils in EPF lesions [143]. Interestingly, basophils also express CRTH2 and CCR3. The aforementioned PGD2-CRTH2 interaction and eotaxin-CCR3 interaction might work in cooperation and thus contribute to the infiltration of both eosinophils and basophils [143]. However, the pathological significance of basophils in EPF is unknown.

Thymus and activation-regulated chemokine (TARC), also known as CCL17, is elevated in serum of EPF patient and correlated to peripheral blood eosinophilia [144]. High serum levels of TARC is also detected in patients with HIV-associated EPF, together with elevated serum levels of eotaxin-3, and CCL27, a molecule mediating homing of lymphocytes to cutaneous sites and involved in T cell mediated inflammation [145]. Further investigation is needed to decipher the possible pathophysiologic roles of these serum markers in the development of EPF.

Clinical Manifestations

Based on the features of eruption appearance and distribution, age of onset, clinical outcome, and associated or causal factors, EPF can be generally divided into three clinical variants: the classic type, the infantile type, and the immunosuppression-associated type that is mainly associated with HIV infection or malignancies (Table 2) [118, 121, 122]. Most cases have peripheral eosinophilia [130, 146]. Elevated serum immunoglobulin E (IgE) levels may be present, but is uncommon in infantile type of EPF [130, 146].

Features of Classic EPF

The classic type of EPF, also known as Ofuji disease [119, 121], has been reported worldwide but most frequently in the Japanese population [122]. Among all the 91 Japanese patients with classic EPF, reported in 1980–2010, the male/female ratio is 2.64:1 [122]. It occurs mainly in adult, with a mean age of onset at 35–40 years, as reported in Asian populations [122, 147].

Classic EPF is clinically characterized by chronic and recurrent clusters of pruritic, sterile follicular papules and pustules arranged in arcuate plaques with central clearing and centrifugal extension [118, 119] (Fig. 11a). These skin lesions typically last more than 1–2 weeks, involute and relapse in an average interval of every 3–4 weeks [118, 119, 121]. The initial lesion most frequently occurs on the face, particularly over both cheeks, where the lesions tend to present as an annular or arcuate configuration [122, 147]. It may also affect the trunk, the extremities, and the scalp [122, 148]. In a few

Table 2 Differences in clinical parameters among the three clinical variants of eosinophilic pustular folliculitis (EPF)

Clinical variants	Associated conditions	Age of onset	Ethnic predilection	Typical skin lesions	Configuration of eruptions	Predilection sites	Systemic symptoms	Elevated serum IgE	Histopathology of skin lesions	First-line treatment
Classic EPF (Ofuji disease)	Rare	35–40 years old on average	Mostly Asians	Clusters of follicular papules and pustules	Annular or arcuate, with central clearing and centrifugal extension	Face, trunk, extremities, and scalp; occasionally palms and soles	None	Variable	Eosinophilic infiltration with spongiosis in the follicular infundibula, with perifollicular involvement	NSAIDs, especially indomethacin
I-EPF	Rare	Less than 1 year old, most within 6 months old	Scarcely Asians	Crusted papulopustules	Isolated or grouped	Scalp; sometimes palms and soles, or widespread	None	Uncommon	Either follicular eosinophilic infiltration, or perifollicular, interfollicular and/or periaxial involvements	Topical steroids, or observation
IS-EPF	HIV infection, or malignancies	Ranging 16–73 years old, mean age 44.2 years	Mostly Asians	Perifollicular erythematous papules and pustules	Less likely to coalesce into plaques or be arranged in an annular configuration	Upper trunk, upper limbs, head and neck (in males); face (in females)	Depending on associated conditions	Variable	Perifollicular infiltration of eosinophils and mast cells, with predominance of CD8+ lymphocytes in the infiltrates	Indomethacin, topical steroids, UVB phototherapy

I-EPF infantile EPF; IS-EPF immunosuppression-associated EPF; IgE immunoglobulin E; NSAIDs nonsteroidal anti-inflammatory drugs; UVB ultraviolet B

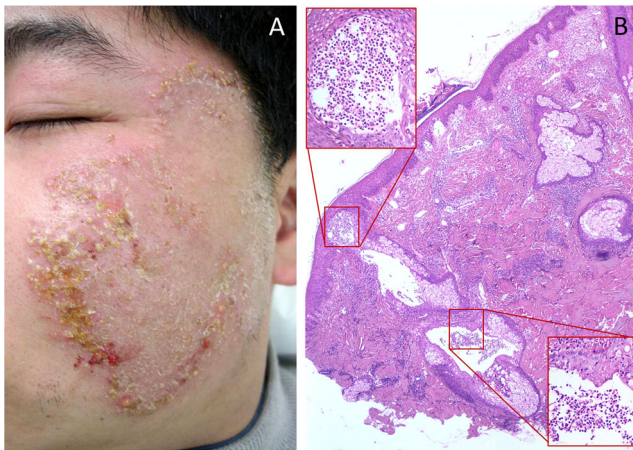


Fig. 11 Eosinophilic pustular folliculitis. **a** A large erythematous plaque with central clearing and peripheral clusters of pruritic follicular pustules arranged in an annular configuration on the left face. Similar lesions kept recurring on both cheeks symmetrically for over 6 weeks in a 23-year-old man. **b** Destruction of follicles and dense infiltrate of eosinophils, lymphocytes and neutrophils in and around follicles and sebaceous glands in the dermis (hematoxylin–eosin, original magnification $\times 40$), with formation of eosinophilic microabscess (red boxes original magnification $\times 400$)

cases, the pustular lesions present on the palms or soles, where follicles are absent [146, 149, 150]. Except for skin involvement, patients with classic EPF are generally in normal health condition with no systemic symptoms [146].

Features of Infantile EPF

The infantile type of EPF, or I-EPF, is a rare variant of EPF that occurs mostly in infants less than 1 year of age [130]. It was first described by Lucky et al. [151] in 1984. I-EPF is scarcely reported in Asian populations, suggesting a possible predisposition associated with ethnic origin [122, 148]. I-EPF occurs in males more than in females [130]. It has an early age of onset, with approximately 70 % of the patients affected within 6 months after birth [130].

I-EPF is characterized by recurrent, isolated, or grouped, crusted papulopustules that are severely pruriginous [130]. These skin lesions have a predilection for the scalp, and may also have widespread involvement [118, 130] or involving the palms and soles [152]. The disease generally runs a benign course, and resolves spontaneously by 3 years of age in over 80 % of cases [130]. It tends to respond well to topical corticosteroid therapy. Patients with I-EPF generally remain in good health without associated diseases, whereas a possible association with atopy has been speculated [130].

Features of Immunosuppression-Associated EPF

The immunosuppression-associated type of EPF, or IS-EPF, is rare and mainly associated with HIV infection, hematological malignancy, or other malignancies [118, 121, 122]. According

to a review of all the 18 Japanese patients with IS-EPF reported in 1980–2010, it has an age of onset ranging 16–73 years, with a mean of 44.2 years [122]. A male predominance is commonly observed [122, 153].

Skin lesions of IS-EPF typically present as perifollicular erythematous papules and pustules, and are intensely itchy [118]. Different from classic EPF, the papular lesions are less likely to coalesce into plaques or be arranged in an annular configuration [122, 153]. Skin lesions of IS-EPF tend to lack the predilection for the face, and are more commonly distributed at nonfacial areas such as the upper trunk, upper limbs, head, and neck [153]. A contrary phenomenon is observed in female patients, among which HIV-associated EPF predominantly affects the face and mimics acne excoriée [154]. Recently, some authors have proposed that hematologic malignancy-associated EPF shows a relatively better response to therapy than HIV-associated EPF, and therefore, should be considered as a unique subtype of EPF [126, 128]. However, this inference requires larger number of clinical cases to validate.

Histopathology

The histopathology of classic EPF is characterized by a prominent eosinophilic infiltration with spongiosis that mainly involves the infundibular region of hair follicles [118, 120, 121] (Fig. 11b). The epidermis around the affected follicles often contains eosinophils and lymphocytes [118]. In the dermis, perifollicular and perivascular infiltration of eosinophils and lymphocytes are common, with perifollicular infiltration more frequently observed in the facial lesions and perivascular infiltration more prevalent in lesions located in nonfacial areas [153]. Perifollicular eosinophilic congregation and formation of eosinophilic microabscess in the follicular infundibula are hallmark findings [118, 121]. Infiltration of neutrophils and basophils are also observed [121, 143]. Follicular mucinosis and exocytosis of inflammatory cells in the hair follicles are strongly associated with facial EPF [153].

In I-EPF, eosinophilic inflammatory infiltration is always present in the skin lesions [130, 155], but true follicular involvement is observed only in 62 % of cases, while many other cases present with perifollicular, interfollicular, and/or periadnexal infiltrates instead [130]. Therefore, a term “neonatal eosinophilic pustulosis” has been proposed as a more appropriate description for this disease [156, 157]. Flame figures, known as a sign of WS, can also be observed in I-EPF occasionally [130].

Studies into the histopathology of IS-EPF are lacking, except for the limited data on some cases associated with HIV infection. HIV-associated EPF is characterized by the predominance of CD8⁺ lymphocytes in the lesional infiltration [118, 121, 123]. Perifollicular infiltration of eosinophils and mast cells are also observed [118, 123, 158].

Diagnosis and Differential Diagnosis

The diagnosis of EPF should be based on a cooperative evaluation of clinical manifestations and histopathological findings. Generally, differential diagnosis of classic EPF includes tinea faciei, Demodex folliculitis, lupus miliaris disseminatus faciei, acne, rosacea, seborrheic dermatitis, granuloma faciale, autoimmune annular erythema, and folliculitis evoked by administration of epidermal growth factor receptor (EGFR) inhibitor [118]. For papules and pustules distributed in nonfacial area, differential diagnosis should also take into account palmoplantar pustulosis, subcorneal pustular dermatosis, and scabies [118].

I-EPF should be distinguished from other causes of pustular eruptions in infants, including erythema toxicum neonatorum, infantile acropustulosis, transient neonatal pustular melanosis, miliaria pustulosa, hyper-IgE syndrome (HIES), Langerhans' cell histiocytosis, bacterial/viral/fungal infection, scabies, and arthropod bites [130, 157, 159, 160].

For IS-EPF associated with hematologic malignancy, skin GVHD should be considered a possible differential diagnosis when eruptions occur after bone marrow or stem cell transplantation [161].

Finally, it should be emphasized that follicular mucinosis and cutaneous T-cell lymphoma, which also have eosinophil infiltrates around the hair follicles or in the upper dermis, are two most important differential diagnoses for EPF, both clinically and histopathologically [118].

Treatment

Individualized therapy should be tailored to different variants of EPF [132]. For classic EPF, treatment with systemic NSAIDs, especially indomethacin, is the first-line therapy and effective in more than 70 % of cases [122]. Although a good response to oral indomethacin treatment is usually achieved within 2–4 weeks, maintenance treatment with indomethacin would be beneficial because relapses are common [147]. For cases intractable to NSAIDs, other treatment options should be considered. These include topical steroids or tacrolimus, ultraviolet B (UVB) phototherapy, psoralen plus ultraviolet A (PUVA), as well as systemic use of corticosteroids, cyclosporine, cetirizine, dapsone, minocycline, dimethyl diphenyl sulfone, colchicine, retinoids, IFN α -2b, and IFN γ , each of which has achieved improvement in a few cases [122, 132, 162]. Recently, Yoshifuku et al. [163] have reported that the daily application of transdermal nicotine patches (6.25–12.5 mg) achieves excellent therapeutic effects with limited side-effects, and might be a potential treatment choice. For the IS-EPF patients recalcitrant to indomethacin and topical steroids, phototherapy with UVB is often curative and should be considered [132, 164].

Different from the other subtypes, infantile EPF does not require the use of indomethacin as a routine treatment, because it tends to resolve spontaneously within several years, and usually responds well to topical steroids [130]. As a result, observation or topical steroid therapy is considered as the first-line treatment for I-EPF [130]. Topical indomethacin or tacrolimus, oral antihistamine, and dapsone, have also been reported to be beneficial in some cases [130, 152]. For recalcitrant cases, oral indomethacin may be considered [152].

Prognosis

Classic EPF and I-EPF are usually considered as benign, although recurrence is frequently observed. It is of special significance to recognize the self-limiting feature of I-EPF so as to avoid unnecessary aggressive treatment in these infants [130, 159, 165]. When making a diagnosis of EPF, one should always keep in mind that a subtype of EPF is associated with HIV infection or malignancies, which would dominant the overall prognosis beyond the skin eruptions and pruritus. Finally, as an important differential diagnosis, the initial lesions of cutaneous T cell lymphoma, although rarely, might share the same clinical and histological findings with EPF and remain misdiagnosed until several years later when the lesions evolve into tumors [118].

Recurrent Cutaneous Eosinophilic Vasculitis

Eosinophilic vasculitis is a term for cutaneous necrotizing vasculitis with predominantly eosinophilic vascular infiltration, in which eosinophils mediate vascular damage in the disease process. This term actually refers to a heterogeneous group of disease entities with similar cutaneous involvement [166]. On one hand, it may be a part of a systemic disease. For instance, eosinophilic vasculitis is associated with connective tissue disease (CTD) in some patients [167]. This group of patients usually presents with pruritic, erythematous or purpuric papules with peripheral blood eosinophilia and hypocomplementemia, and are generally responsive to corticosteroids [167]. Eosinophilic vasculitis is also reported to be a cutaneous involvement of other systemic diseases such as rheumatic arthritis [168] and hypereosinophilic syndrome [169]. On the other hand, an idiopathic entity of eosinophilic vasculitis, commonly known as recurrent cutaneous eosinophilic vasculitis (RCEV), usually presents as recurrent episodes of characterized skin lesions without systemic organ involvement or significant immunoserologic findings [170]. RCEV is a rare type of cutaneous necrotizing vasculitis of small dermal vessels characterized by almost exclusively eosinophilic infiltration with minimal or no leukocytoclasia [171]. This entity was first described by Chen et al. [170] in 1994. To the best of our knowledge, there have been only ten

patients with RCEV reported in the English literature, and three in the Chinese literature. Here, we describe this peculiar disease, RCEV, in detail.

Etiology and Pathogenesis

RCEV is a rare disease of unknown origin [172]. The predominant infiltration of eosinophils is considered to play important roles in the development of the small-vessel necrotizing vasculitis in skin lesions of this disease [171]. Very few studies into this entity have been documented thus far. Marked deposition of eosinophil granule major basic protein (MBP), a cytotoxic protein abundantly expressed in eosinophils and mediating many eosinophil-associated immune functions, has been detected in the affected vessel walls by immunofluorescence studies [170, 171]. Vascular cell adhesion molecule-1 (VCAM-1), an endothelial adhesion molecule that supports eosinophil adhesion [173], has been demonstrated to be expressed on the endothelium of the affected vessels [170, 171]. It is also proposed that the eosinophilia in RCEV might be dependent on the concentrations of serum interleukin-5, a Th2 cytokine released by CD4⁺ T cells [170, 174].

Clinical Manifestation

RCEV is a rare disease that has not been identified as a distinct entity until 20 years ago [170]. Only ten cases with RCEV have been reported in the English literature, and three in the Chinese literature. These patients are reported from the USA [170], France [175], Greece [176], and Asian countries including China [172, 177–179], Japan [174, 180, 181], and Thailand [182], respectively. All the 13 patients reported are adults, most of which are middle-aged (40–60 years old) or elderly (at least 70 years old), whereas only two are young (17 and 18 years old, respectively). Five of them are male patients, and eight are female.

RCEV is clinically featured as recurrent, multiple, pruritic, and sometimes swelling, skin lesions with a chronic, relapsing course. Different types of skin lesions can be present, including annular urticarial plaques, erythematous or purpuric papules/plaques, angioedema, palpable purpura, and occasionally, hemorrhagic vesicular lesions [170, 172]. These are often associated with peripheral blood eosinophilia, although the eosinophil count does not always parallel the severity of the disease [170]. Generally, no systemic disease is associated with RCEV [170–172], with the exception of one case reported as RCEV coexisting with a latent chronic periaortitis (CP) [176], which is a disease commonly known as retroperitoneal fibrosis (RPF) and characterized by inflammatory involvement of the outer layer of the aorta and surrounding tissues [183].

Most patients with RCEV respond promptly to treatment with systemic corticosteroids. However,

maintenance treatment is needed because skin lesions frequently recur [170, 174].

Histopathology

The typical histopathological findings of RCEV are necrotizing vasculitis of small vessels in the dermis, with exclusively eosinophilic infiltration and minimal or no leukocytoclasia [170, 171]. The small-vessel necrotizing vasculitis and fibrinoid degeneration on small-vessel walls are featured for RCEV, which are distinct from that of other eosinophilic cutaneous disorders such as episodic angioedema with eosinophilia, WS, and hypereosinophilic syndrome [171, 181].

Diagnosis and Differential Diagnosis

Establishment of a diagnosis of RCEV is based on typical clinical manifestations and histopathology, and exclusion of parasite infection with gnathostomiasis and systemic diseases, especially connective tissue diseases (CTDs) and Churg–Strauss syndrome [166]. Besides these, the common differential diagnosis should also include drug eruption, urticaria, late-phase urticaria, urticarial vasculitis, episodic angioedema with eosinophilia, Wells syndrome, and hypereosinophilic syndrome [172, 181].

Treatment

Systemic glucocorticoids treatment usually achieves quick and effective response, and is considered as the mainstay treatment [172]. Prednisone at 15–30 mg daily, or equivalent, could be attempted as a starting dose [174, 181]. However, relapse often occurs during the dose-tapering process, and thus requiring a maintenance treatment [170]. Sakuma-Oyama et al. [180] reported a case successfully treated by adjuvant therapy with suplatast tosilate. Tanglertsampan et al. [182] treated another case, a 53-year-old man, efficaciously with indomethacin. More recently, Sugiyama et al. [174] tried with oral tacrolimus in an 80-year-old female patient that was corticosteroid-dependent, and then successfully controlled the disease with much lower maintenance dose of prednisolone. It is therefore suggested that tacrolimus may be a reliable salvage therapy for corticosteroid-dependent patients with RCEV, although its possible adverse effects should also be taken into consideration [174].

Eosinophilic Fasciitis

Eosinophilic fasciitis (EF) is an uncommon connective tissue disease characterized by symmetrical painful swelling with a progressive induration and thickening of the skin and soft tissues of the distal extremities, with uncertain etiology

[184]. This entity was first described by Shulman in 1974 as a new syndrome defined by scleroderma-like induration of the skin associated with peripheral eosinophilia, hypergammaglobulinaemia, and elevated erythrocyte sedimentation rate (ESR) [185]. More than 300 cases, most sporadic rather than epidemic, have been reported thereafter [186].

Etiology

The exact cause of EF remains uncertain, whereas hypotheses of different causal or associated factors have been proposed [184]. First of all, a history of intense physical exertion or trauma prior to EF onset is present in approximately 30–46 % of patients with EF, suggesting a possible causal role of muscle trauma in this disease [82, 187].

Second, drugs and chemical compounds are proposed to be triggering factors in some EF patients. These patients are reported to have EF onset after the use of natalizumab (a humanized monoclonal antibody against the cell adhesion molecule α 4-integrin) [188], influenza vaccination [189], simvastatin, atorvastatin, ramipril, phenytoin, or subcutaneous heparin, or after the exposure to trichloroethylene [184, 186].

Third, hematological disorders are frequently reported to be associated with EF [186]. Briefly, less than 10 % of EF patients have an underlying hematological disorder such as thrombocytopenia, aplastic anaemia, myelomonocytic leukemia, chronic lymphocytic leukemia, myeloproliferative disorder, and scarcely, paroxysmal nocturnal hemoglobinuria [190], chronic eosinophilic leukemia, not otherwise specified (CEL-NOS) [191], lymphoma [192], and multiple myeloma [184, 186, 193].

Finally, there are few sporadic reports on other possible triggering factors including infections (e.g., borreliosis [194], *Mycoplasma arginini* infection [195]), arthropod bites (e.g., fire ant bites [196]), physical factors (e.g., radiotherapy, burns) and allogeneic hematopoietic stem cell transplantation (HSCT), as well as other associated diseases such as solid tumors (e.g., prostatic cancer, breast cancer, bronchopulmonary cancer, choroidal melanoma), autoimmune diseases (e.g., Hashimoto's thyroiditis, Graves disease, Sjögren syndrome, systemic lupus erythematosus, primary biliary cirrhosis), and rarely, graft-versus-host disease (GVHD) [184, 186, 193, 197].

Pathogenesis

The pathogenetic mechanisms of EF remain unknown, although it is generally considered as an entity in the broad spectrum of connective tissue diseases, in which abnormal immune mechanisms should play fundamental roles [184]. Some findings provide supporting evidence for this speculation of abnormal immune pathogenesis. For instance,

deposition of IgG and C3 in affected fascia, and hypergammaglobulinemia, are detected in patients with EF [187, 198]. Elevated serum levels of soluble CD40 ligand (sCD40L), which have been reported to be possibly involved in the mechanisms of various connective tissue diseases including systemic sclerosis [49, 199] and systemic lupus erythematosus [199, 200], are also detected in patients with EF and are suggested to be potential markers for the disease activity [201]. Matrix metalloproteinase-13 (MMP-13), a member of the collagenase family that is implicated in the pathogenesis of systemic sclerosis by participating in the extracellular matrix remodeling, has recently been identified to be decreased in serum level in patients with EF [202], whereas the serum level of tissue inhibitor of metalloproteinase 1 (TIMP-1) is elevated significantly in EF [203].

Infiltration of lymphocytes and eosinophils also participate in the pathogenic mechanisms. Immunohistochemistry analysis of biopsy tissues has identified, in 10 out of 11 patients with EF, a predominancy of macrophages and CD8+ T lymphocytes (CD4/CD8 ratio < 1) with few eosinophils in the inflammatory infiltrates of fascia tissues [204]. Some of these CD8+ lymphocytes contain granzyme B, thus suggesting a cytotoxic cellular immune response in EF, which could be triggered by infectious or environmental agents [204]. On the other hand, eosinophil activation and degranulation can result in release and tissue accumulation of eosinophil granule proteins, and thus contribute to the development of pathologic fascia fibrosis [184, 186].

Clinical Manifestation

EF affects males and females almost equally [187, 205]. It has been reported in both adults and pediatric population [82, 206], although the middle-aged group is most likely to be affected [82, 187, 205].

EF usually presents as an abrupt onset of painful, erythematous swelling and stiffness of the upper or lower extremities or both. In most cases, involvement of the extremities is symmetrical, whereas unilateral involvement occasionally occurs [189]. Pitting edema can progressively be replaced by thickening and induration of the skin, showing the characteristic skin signs such as the “groove sign” (a depression appearance along the course of a vein or between muscle groups) (Fig. 12a) and the “peau d’orange” sign with hyperpigmentation [82, 187]. Severe skin induration and fascia fibrosis frequently result in joint contracture and tendon retraction, showing the prayer sign, the inability to close a fist or restricted joint movement [186].

These cutaneous changes may also affect the trunk or the neck in some patients [82, 187]. Morphea-like lesions are frequently found (Fig. 12b), and considered to be a risk factor for residual fibrosis or poorer prognosis [82, 187, 193]. In late stage, extensive skin fibrosis of the trunk may even lead to

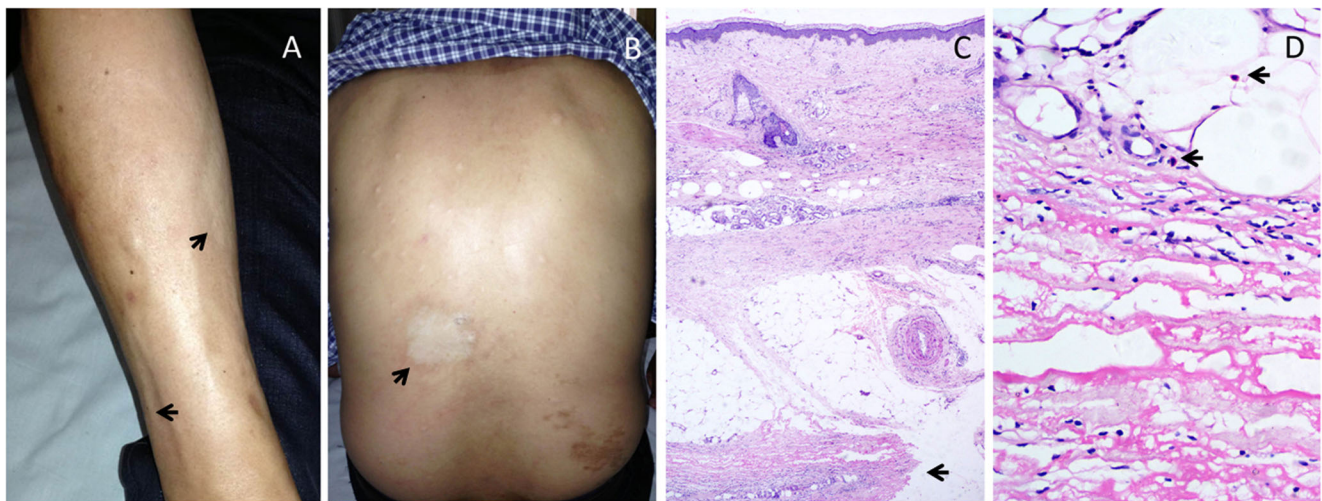


Fig. 12 Eosinophilic fasciitis. **a** Symmetrical, painful swelling and stiffness of the extremities with skin itching for 3 months in a 49-year-old man, with visible depression appearance between muscle groups (“groove sign”) on the forearms (see *arrows*). **b** An asymptomatic, morphea-like patch on his back (see the *arrow*). **c** Inflammatory and

fibrous thickening of the fascia (see the *arrow*) (hematoxylin–eosin, original magnification $\times 40$). **d** Infiltrate of lymphocytes and few eosinophils (see *arrows*) in the fascia (hematoxylin–eosin, original magnification $\times 400$)

progressive respiratory limitation due to the restriction of chest movement and reduced expansibility of chest wall, a status also known as “hidebound chest” [207].

Systemic symptoms, such as spontaneous or provoked myalgia, weight loss, and asthenia, are common in patients with EF, but nonspecific [193]. Many patients have a history of intense physical exertion prior to the onset of the disease [187, 193, 205]. Another common manifestation of EF is articular involvement. Inflammatory polyarthritis causing arthralgia and morning stiffness, as well as carpal tunnel syndrome, are frequently reported [187, 193]. It has also been reported that peripheral polyneuropathy is a complication of EF in one patient, which lasted for 6 months after the extremity swelling and tenderness improved upon treatment [208].

Visceral involvement is absent in almost all patients with EF [82, 184, 187, 205], whereas very few exceptions have been reported to be complicated by pleural effusion [209], pericarditis [210], and renal involvement [211]. Noteworthy, sclerodactyly, Raynaud’s phenomenon, and the abnormal capillaroscopy findings featured for systemic sclerosis (SSc), are usually absent in EF, which helps to differentiate from this disease [187, 193, 212].

Finally, some EF patients have an associated disease such as hematological disorder, solid tumor, or autoimmune disease, and thus may also present with clinical manifestations of the relevant disease.

Laboratory and Imaging Findings

Typical laboratory findings in patients with EF include peripheral eosinophilia, elevated serum levels of CRP and ESR, hypergammaglobulinemia, and low titers of antinuclear antibodies (ANA) without detectable anti-extractable nuclear

antigen (anti-ENA) antibodies [187, 193, 213]. However, it should be noted that none of these markers are present in all patients [184]. Additionally, the peripheral blood eosinophil counts do not correlate with disease severity, and is not useful for evaluation of treatment response or follow-up [184, 186, 187]. Referring to the muscle enzymes, an increased serum level of aldolase with a normal level of creatinine kinase (CK) has been reported as a possible feature of EF, and suggested as a useful indicator of disease activity [206, 214, 215], although this speculation needs further validation in large sample size.

Medical imaging is of great value in examining the fascia involvement and helping with the diagnosis of EF. Magnetic resonance imaging (MRI) of the involved extremities serves as the best option [216, 217]. The characteristic MRI findings consist of abnormal fascial signal intensity and enhancement, both of which are directly proportional to disease activity in EF [216–219]. Therefore, MRI can also be a valuable aid in evaluating response to treatment and in patient follow-up [216, 217]. Ultrasonography findings in EF have been reported to show a possible correlation with MRI, and thus can be considered as an alternative imaging evaluation modality [220, 221].

Histopathology

Evaluation of the histopathology basically requires a full-thickness, or skin-to-muscle, wedge biopsy [186, 187]. The characterized histopathological findings of EF are the inflammatory and fibrous thickening of fascia, usually 2 to 15 times thicker than normal, with inflammatory infiltrates mainly composed of lymphocytes and/or eosinophils [82, 187, 193, 213] (Fig. 12c–d). The infiltrates in the fascia are mainly composed of macrophages and CD8+ T lymphocytes (CD4/CD8

ratio <1), which is demonstrated by immunohistochemistry [204]. Eosinophil infiltrates are present in the majority of patients but not all, and can become absent in a chronic phase of the disease or after corticosteroid treatment [186]. The epidermis and dermis are usually unaltered or mildly affected. Nevertheless, dermal involvement can be observed in morphea-like skin lesions, where dermal collagen may be mildly sclerotic [193]. Perimyositis, the inflammatory involvement of the epimysium near the fascia and the perimysium among muscle fibers, are also frequently complicating the pathological changes [222].

Diagnosis and Differential Diagnosis

Patients presenting with swelling, induration, and thickening of the skin and subcutaneous tissue on extremities, with associated histopathological findings showing fascial thickening and inflammatory infiltration of lymphocytes and macrophages, with or without eosinophilic infiltration, should lead to a tentative diagnosis of EF. Pinal-Fernandez and colleagues [184] have recently published their proposed criteria for the diagnosis of patients with EF, in which they emphasize the characteristic clinical manifestations and histopathological findings as two most important factors for diagnosis. Therefore, a full-thickness skin biopsy is almost mandatory [184, 186]. Muscle MRI examination is of great value for evaluating the morphological changes of the lesional fascia and assisting the diagnosis [216]. Laboratory findings such as peripheral eosinophilia, hypergammaglobulinemia, elevated ESR and CRP, as well as increased aldolase, may lend support to the diagnosis of EF, but are not required or sufficient to establish the diagnosis [184].

Differential diagnoses usually include systemic sclerosis, eosinophilia-myalgia syndrome (EMS) after L-tryptophan ingestion, Churg–Strauss syndrome, and hypereosinophilic syndrome [186]. Some rare conditions, such as silica exposure [223], peripheral T cell lymphoma with skin and fascia involvement [186], and extremity swelling caused by cutaneous metastatic malignancy, should also be ruled out. Finally, it is also noteworthy that some patients with EF may be in concurrence with hematological disorders, solid tumors or other autoimmune diseases, which should not be neglected after establishing a diagnosis of EF.

Treatment

Systemic corticosteroid treatment is generally effective and recommended as a standard therapy for EF [184, 186]. The commonly used, effective dose is 0.5–1 mg/kg daily [186]. A partial or complete response is achieved in most patients (70–90 %) with EF by treatment with corticosteroids [187, 193]. Importantly, the use of methylprednisolone pulses (0.5–1 g daily for three consecutive days) at initiation of treatment

may lead to a markedly better outcome and higher rates of complete remission, and therefore should be considered for a certain number of patients [186, 187, 193]. However, cases with residual symptoms after many months of corticosteroid treatment have been reported [187, 193].

An immunosuppressant or immunomodulating agent should be combined to corticosteroids for patients with resistance or dependency to corticosteroids [186]. These include not only the classic choices such as methotrexate, azathioprine, cyclophosphamide, cyclosporine, and dapsone [186], but also the more recently available agents such as anti-CD20 monoclonal antibody (rituximab) [224] and anti-TNF α (infliximab) [225]. Among these immunomodulating agents, methotrexate at low doses (15–25 mg once weekly) is probably the most favored second-line treatment, and is peculiarly recommended, in combination with steroids, for patients with morphea-like lesions [184, 187, 193].

Other therapeutic modalities, such as psoralen-ultraviolet A bath photochemotherapy (PUVA) [226], and extracorporeal photochemotherapy [147] are also reported to have gained improvement in several patients with EF. Furthermore, for an EF patient with a hematological disorder or other disease, treatment targeting this associated disorder is also required and probably beneficial to the remission of EF [227].

Prognosis

EF is generally a benign disease, with an exception that a few patients are associated with malignancies [184]. Some patients experienced spontaneous improvement of EF, although this is extremely rare [187]. Most patients are highly responsive to corticosteroid treatment, but quite a proportion of patients would still progress to incomplete remission with residual cutaneous fibrosis even after standard treatment. Several factors have been suggested to be associated with the prognosis, with regard to the outcome of residual fibrosis. Firstly, a young age (under 7 or 12 years old) at the time of onset, trunk involvement, and the occurrence of morphea-like skin lesions are found associated with a poor outcome with residual fibrosis [205]. On the other hand, earlier initiation of therapy [205] and the use of methylprednisolone pulses at initiation of treatment [186, 193] lead to a better outcome. Especially for patients with morphea-like skin lesions, the use of methotrexate as a second agent to combine with steroids is proposed for a better prognosis [186].

Take-Home Messages

- (1) Eosinophilic dermatoses are characterized by eosinophil infiltration and/or degranulation in skin lesions, with or without blood eosinophilia. Allergy-related dermatoses,

parasitic infestations, and bullous pemphigoid are most common.

- (2) Eosinophilic cellulitis (Wells syndrome) is histologically characterized by flame figures. Patients may occasionally have an associated hematologic malignancy, Churg–Strauss syndrome or hypereosinophilic syndrome, and should be diagnosed and managed with caution.
- (3) Granuloma faciale (GF) has unique histological changes characterized by a Grenz zone. Dermatoscopy can assist diagnosis and differential diagnosis. GF is long-lasting, and notoriously recalcitrant to treatment. Topical tacrolimus and laser may be promising treatments.
- (4) Eosinophilic pustular folliculitis (EPF) is characterized by folliculotropic infiltration of eosinophils. Oral indomethacin is usually effective. An immunosuppression-associated subtype of EPF is notable, which is associated with either HIV infection or malignancies.
- (5) Eosinophilic vasculitis is a condition, either secondary to a systemic disease such as connective tissue disease, or idiopathic, known as recurrent cutaneous eosinophilic vasculitis (RCEV).
- (6) Eosinophilic fasciitis (Shulman disease) is an uncommon connective tissue disease. A skin-to-muscle biopsy with muscle MRI examination greatly assists the diagnosis. Less than 10 % of the patients have an underlying hematological disorder.

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