Erythroderma

19

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Background

Erythroderma is a severe and potentially life-threatening dermatitis described as an intense and widespread erythema typically involving greater than 90% of the body surface area, with a variable degree of exfoliative skin scaling (see Figs. 19.1 and 19.2) [1, 2]. It is a manifestation of a wide range of cutaneous and systemic diseases including infection, malignancy, and drug hypersensitivity reactions [3].

There are numerous systemic and cutaneous diseases known to be associated with erythroderma (Tables 19.1 and 19.3). The most common trigger of erythroderma is an exacerbation of an underlying dermatitis, most commonly psoriasis (Fig. 19.3) (23%), atopic dermatitis, and contact dermatitis [4–7]. Drug reaction is another important cause of erythroderma, implicated in 20% of cases, with at least 135 drugs suspected as potential causative agents [5–8, 10]. A common malignancy associated with erythroderma is cutaneous T-cell lymphoma (CTCL) [3, 7, 9]. Idiopathic erythroderma, where no cause can be elucidated despite thorough serial investigations, occurs in approximately 30% of cases. "Red man's syndrome" associated with rapid vancomycin infusion is considered to be an example of idiopathic erythroderma [3–5, 8, 10, 11].

Because erythroderma is often associated with scaling and extensive erythema, it is often difficult to discern the typical features characteristic of the preexisting, underlying condition. For this reason, diagnosis and management strategies can be challenging [1, 2].

Erythroderma is thought to be mediated by a complicated process of inflammatory cell interactions, resulting in a dramatic turnover of epidermal cells [12]. It is a rare condition, with an incidence rate of approximately 1 per 100,000 adults [13].

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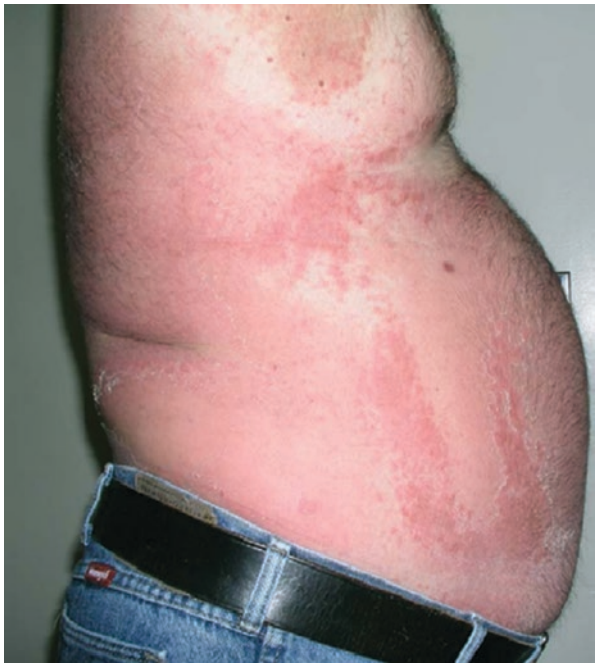

Fig. 19.1 Widespread erythema and areas of sparing in a patient with unclear etiology of erythroderma. (Used with permission from Rothe et al. [3])

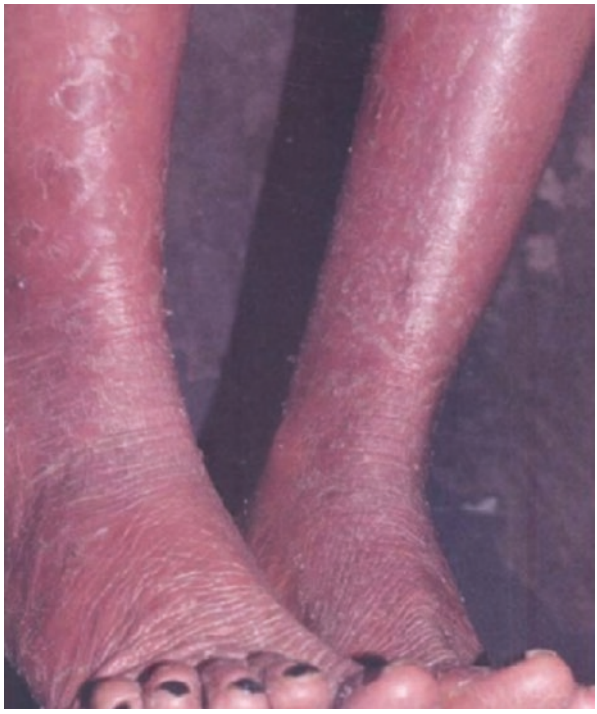

Fig. 19.2 Diffuse erythema and scaling of a 14-year-old girl with erythroderma of unknown etiology. (Source (open access): https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2800861/)

Table 19.1 Common causes of erythroderma (remembered by mnemonic IDSCALP) [54]

I	*Idiopathic – 30%* *Infections* (HIV, HSV, dermatophytosis, scabies)
D	*Drug allergy – 20%*
S	*Seborrheic dermatitis – 2%* *Sarcoidosis*
C	*Contact dermatitis – 3%* *Connective tissue diseases*
A	*Atopic dermatitis – 10%* *Autoimmune* (systemic lupus/dermatomyositis/bullous pemphigoid/pemphigus foliaceus/lichen planus/graft vs host disease)
L	*Lymphoma and leukemia – 14%* (including Sezary syndrome)
P	*Psoriasis – 23%* (including reactive arthritis/pityriasis rubra pilaris)

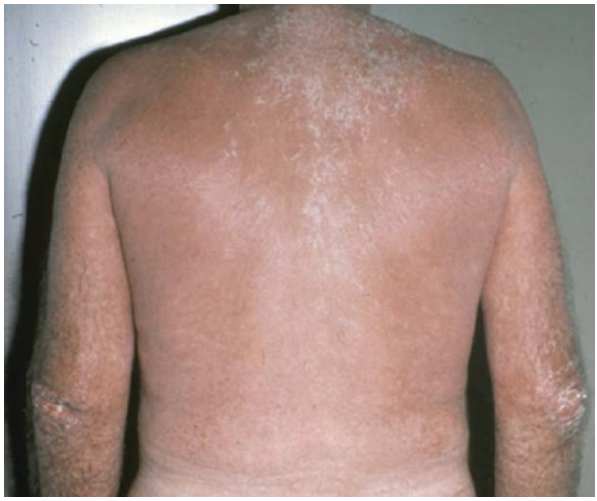

Fig. 19.3 Patient with erythrodermic psoriasis and classic plaques on elbows. (Used with permission from Rothe et al. [3])

Erythroderma is rare in children and occurs at an average age of 42–61 years [14]. When age of onset is less than 40 years, the condition is typically a result of atopic dermatitis, seborrheic dermatitis, staphylococcal scalded skin syndrome, or a hereditary ichthyosis [14, 15]. It is more common in males and has no racial predilection [3–7, 9, 16].

Classic Clinical Presentation

The typical presentation of erythroderma is characterized by erythematous patches which progressively increase in size and coalesce to cover most of the body's surface, with occasional islands of sparing [17]. Scaling can occur as large sheets or small flakes and generally erupt 2–6 days after the onset of erythema. Pruritus is common and is most severe in patients with atopic dermatitis and Sezary syndrome

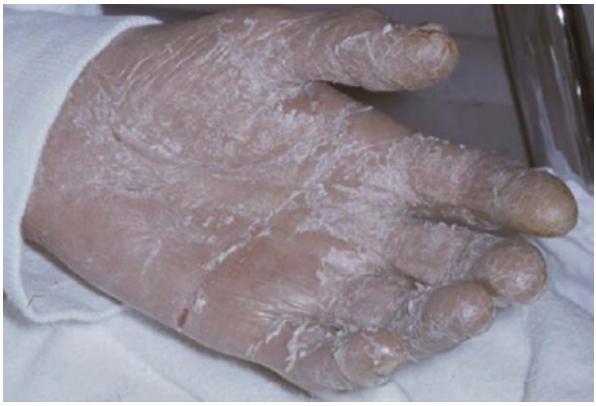

Fig. 19.4 Patient with Sezary and skin fissuring. (Used with permission from Rothe et al. [3])

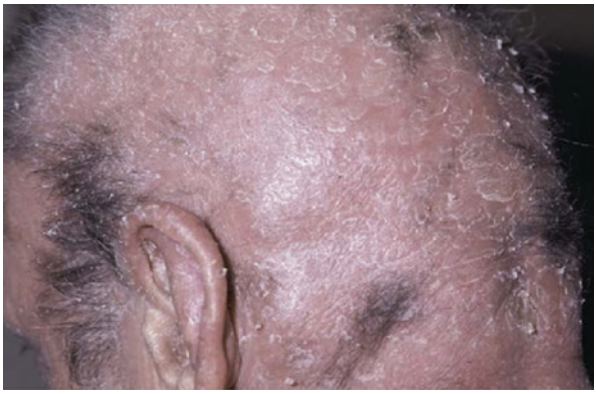

Fig. 19.5 Diffuse alopecia in a patient with chronic idiopathic erythroderma. (Used with permission from Rothe et al. [3])

(a leukemic variant of cutaneous T-cell lymphoma where atypical lymphocytes known as Sezary cells are found in peripheral blood; see Fig. 19.4) [50]. The skin may feel leathery secondary to excessive scratching and there may be eyelid and periorbital involvement [18].

Especially in chronic conditions, patches of hypopigmentation can be observed, and hair and nails may shed [19]. Nails may also become ridged, thickened, and brittle [9, 17, 20, 21]. Individuals with long-standing erythroderma may present with cachexia, vitiligo, diffuse alopecia (see Fig. 19.5), and thickened palms and soles (Table 19.2) [18, 22].

Atypical Presentation

Table 19.2 Classic features of erythroderma

Skin	Widespread erythema Variable degree/character of scaling (2–6 days after erythema) Pruritus (can lead to lichenification)
Eyes	Eyelid swelling may lead to ectropion (eyelid eversion), blepharitis, epiphora (excessive tearing), ectropion (eyelid eversion)
Palms/soles	May develop yellowish, diffuse keratoderma
Nails	Dull, ridged, thickened May develop onycholysis and shed (onychomadesis)
Lymph nodes	Generalized lymphadenopathy which may be reactive or suggestive of lymphoma
Hair	Telogen effluvium (scaling of the scalp) leading to varying degrees of hair loss

Table 19.3 Uncommon causes of erythroderma

Stevens-Johnson syndrome
Toxic epidermal necrolysis
Toxic shock syndrome
Stasis dermatitis (venous eczema)
Seborrheic dermatitis
Staphylococcal scalded skin syndrome
Blistering diseases including pemphigus and bullous pemphigoid
Sezary syndrome
Rare congenital ichthyotic conditions

Associated Systemic Symptoms

Systemic symptoms related to erythroderma itself or to the primary disease can be observed. Many of these features can lead to serious sequelae and are discussed further in the complications section. Patients often are unwell appearing and report chills, fever, fatigue, and malaise. Lymphadenopathy and (rarely) splenomegaly can be observed. Hepatomegaly is seen in 1/3 of cases and is most common in drug-induced erythroderma [7, 22]. Significant protein loss exceeding 9 g/m^2 body surface per day as a consequence of skin exfoliation can lead to hypoalbuminemia, edema, and muscle wasting [12]. As a result, patients may experience loss in temperature regulation and up to 50% of patients develop pretibial and pedal edema [2, 3].

When erythroderma occurs secondary to drug reaction, eosinophilia can be observed along with systemic symptoms characteristic of DRESS (drug reaction and systemic symptoms; see Chap. 20) [2].

Time Course of Disease

Erythroderma may develop rapidly over hours to days or more gradually over weeks to month (see Table 19.4) [22]. Patients may initially present as medically stable or with life-threatening complications [3].

The duration of erythroderma is highly variable and is determined by the underlying cause. Erythroderma as a result of primary skin disease is typically a gradual course with a median duration of 10 months but can go on to last years [7].

The disease evolves more rapidly when it is a result of drug hypersensitivity reaction, lymphoma, or leukemia. In the setting of systemic disease, symptoms may persist from weeks to years – dependent on the course of the underlying disorder. Conversely, in the case of drug-induced erythroderma, resolution of disease can occur in as little as 2–6 weeks after discontinuation of the offending agent [3]. Patients with DRESS, however, may take longer to recover – over weeks to months with possible relapse (*see* Chap. 20).

Common Mimics and Differential Diagnosis

The diagnosis of erythroderma is difficult given it is usually a manifestation of an underlying diagnosis or exacerbation of primary disorder (Table 19.5). Additionally, the characteristic physical findings of erythroderma generally obscure underlying disease features.

Key Physical Exam Findings and Diagnosis Features

As the list of causative factors of erythroderma continues to expand, it becomes more difficult to pinpoint the precipitating diagnosis [22]. Because of this, a thorough history of presenting illness is of utmost importance in diagnosing erythroderma [23]. Patients must be asked about all medications, preexisting medical conditions, allergies, and previous diagnoses of rash and skin disorders [7, 22].

Table 19.4 Typical course of disease according to etiology [22]

	Onset	Features	Duration
Primary cutaneous	Slower/ indolent	Erythematous patches of increasing size with variable islands of sparing Subsequent scaling	Variable
Drug-induced	Abrupt	Morbilliform or urticarial followed by erythematous patches which increase in size	Comparatively quick resolution
Systemic	Gradual	Initially characteristic of disease before patches form and coalesce	Variable
Idiopathic			Unpredictable

Table 19.5 Common mimics of erythroderma, often implicated as precipitating factors

Acanthosis nigricans
Allergic contact dermatitis
Bullous pemphigoid
Contact dermatitis
Cutaneous T-cell lymphoma
Familial benign pemphigus (Hailey-Hailey disease)
Graft-versus-host disease
Lichen planus
Malignancy
Pediatric atopic dermatitis
Pemphigus foliaceus
Pityriasis rubra pilaris
Plaque psoriasis
Reactive arthritis
Rapid vancomycin infusion
Sarcoidosis
Seborrheic dermatitis
Stasis dermatitis

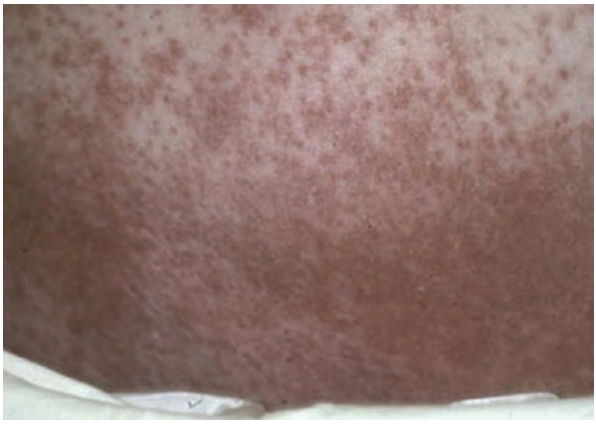

Fig. 19.6 Elderly patient with near erythroderma. Microscopy confirmed scabies infestation. (Used with permission from Rothe et al. [3])

Physical examination is crucial in attempts to detect an underlying etiology as well as to evaluate for systemic involvement and potential complications (i.e., organomegaly, lymphadenopathy, peripheral edema, infection, heart failure, and potential respiratory compromise) [7, 18, 24].

Following a detailed history and physical, a skin biopsy, laboratory studies, imaging, and histology may useful adjuncts to derive a definitive diagnosis and exclude clinical mimics (see Fig. 19.6). These ancillary studies are often nonspecific, although with repeat testing the diagnosis may become apparent over time (Table 19.6) [11, 15, 16].

Table 19.6 Diagnostic features of underlying disorders

Skin exam features [3, 18, 26]	Blisters and crusting: secondary infection, autoimmune blistering disorders (bullous pemphigoid, pemphigus foliaceus Large scales: psoriasis Fine scales: atopic dermatitis/dermatophyte infection Burn-like scale: seborrheic dermatitis Islands of sparing/yellow tinge to the skin/hyperkeratosis of the palms and soles: pityriasis rubra pilaris (PRP)
Laboratory testing	Leukocytosis, increased ESR, anemia, hypoalbuminemia, and hyperglobulinemia are frequent findings in all causes Eosinophilia in patients with DRESS Increased IgE may be noted in atopic dermatitis Consider peripheral blood smears and bone marrow examination if leukemia is considered
Skin biopsy	Consider if cause unknown although tend to be nonspecific Repeated biopsies may be necessary Skin scrapings may show hyphae or mites
Imaging [22]	If cause is unknown, imaging may be performed as a survey for occult malignancy Chest radiograph can identify infections, inflammatory disorders such as sarcoidosis with hilar lymphadenopathy, and congestive heart failure
Cultures/PCR	Evaluation for suprainfection, fungal infections, herpes simplex virus, and varicella zoster virus
Histological [27–30]	In all comers, hyperkeratosis, acanthosis, spongiosis, and perivascular inflammatory infiltrate are frequent findings in general May otherwise be nonspecific
Immunofluorescence [22, 31]	Of benefit in autoimmune blistering disease or connective tissue disease (i.e., immunoglobulins at the dermal-epidermal junction)

Management

Erythroderma is a dermatologic emergency which requires a dermatology consultation and hospital admission for severe cases to avoid potentially catastrophic complications. The principle management consists of discontinuation of all offending medications, maintaining skin moisture and integrity (through aggressive wound care), adequate hydration and nutrition, electrolyte repletion, and antibiotics for secondary infection (Table 19.7). Erythroderma as an isolated process will persist until the underlying condition is addressed, and the primary etiology may impact disease course and management options. Therefore, once the underlying diagnosis is established,targeted therapy should be administered promptly (Table 19.8).

If a cause can be identified, then specific treatment should be initiated. Notably, systemic steroid should be avoided in psoriasis and staphylococcal scalded skin syndrome.

Table 19.7 Initial management

Systemic symptoms [3]	Replacement of fluid and electrolytes Monitoring hemodynamic status Monitoring and regulation of body temperature Nutritional support Treatment of skin inflammation and pruritus Discontinuation of all offending/unnecessary medications Diuretics for refractory edema
Skin inflammation and pruritus [3, 22, 32]	Topical corticosteroids and oral antihistamines Oatmeal baths or warm wet compresses (no more than a quarter of the body at a time) Bland emollients or petrolatum for patient comfort
Infections	Blood cultures Broad-spectrum antibiotic coverage (to include MRSA) Antiviral medications where appropriate

Table 19.8 Targeted treatment modalities

Atopic dermatitis [22, 33–36]	Avoiding allergens Topical and systemic steroids In refractory cases: cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, and/or interferon
Psoriasis [37–40, 51–53]	Topical steroids Phototherapy Methotrexate Retinoids (i.e., acitretin) Cyclosporine In refractory cases: tumor necrosis factor (TNF) inhibitors, interleukin (IL) inhibitors, phosphodiesterase type 4 [PDE-4] inhibitors (i.e., infliximab, adalimumab, etanercept, ustekinumab, secukinumab) *this therapy can cause mycosis fungoides to progress
Mycosis fungoides [41–45]	Topical corticosteroids Topical chemotherapy Topical retinoids May consider phototherapy and radiotherapy In refractory cases: interferon, oral retinoids, histone deacetylase inhibitors, monoclonal antibodies, photopheresis, and chemotherapy Rarely stem cell transplantation considered
Cutaneous T-cell lymphoma [25]	Methotrexate Potent topical steroids Chemotherapy UV light
Sezary syndrome [46]	Extracorporeal photochemotherapy Systemic retinoids Interferon
Pityriasis rubra pilaris (PRP) [22, 47]	Systemic retinoids as first line Topical steroids as adjunct to palms, soles, face, skin folds, and extremities May consider *methotrexate*, TNF-alpha inhibitors, *cyclosporine*, and azathioprine
Drug induced [2, 7, 35]	Discontinue causative agents Short-course oral steroids or pulse intravenous IV steroid therapy
Idiopathic erythroderma [1, 5, 9, 11]	Low to mid-potency topical corticosteroids Oral antihistamines In refractory cases: systemic corticosteroids

Complications

While the physiologic demands of erythroderma are tolerated by many patients, those at the extremes of age and patients with multiple comorbidities may suffer life-threatening consequences (see Table 19.9). The shunting of blood through the skin due to peripheral vasodilation can result in high-output heart failure [3]. These patients can present with tachycardia and pulmonary edema. Increased skin perfusion also results in temperature dysregulation and fluid and electrolyte imbalance. Exfoliation and protein loss result in edema and leave patient's susceptible to secondary infections [12]. Acute respiratory distress syndrome (ARDS) is also a common complication.

End-organ damage may develop such as hepatitis, myocarditis, and/or interstitial nephritis [2].

Mortality rates range between 4 and 64% depending on the patient population [7, 22].

Bottom Line: Erythroderma Clinical Pearls

In the majority of cases, erythroderma results from an underlying condition and cannot itself be prevented [22]. Individuals who develop erythroderma as a result of drug hypersensitivity should be instructed to avoid the offending agent in the future. Erythroderma as a result of underlying inflammatory skin condition will usually abate with treatment but may recur at any time. Idiopathic erythroderma is characterized by a more unpredictable course. Overall, prognosis of erythroderma is dependent on the underlying cause and is generally favorable if the underlying disease can be effectively treated [48–50].

Table 19.9 Physiologic derangements

Protein loss
Edema
Hypoalbuminemia
Fluid loss
Temperature dysregulation
Electrolyte and metabolic disturbances
High output cardiac failure
Sepsis from superinfection

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