Erythroderma/exfoliative dermatitis: a synopsis

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Introduction

Exfoliative dermatitis is an extreme state of skin irritation resulting in extensive erythema and/or scaling of the body. Several skin disorders may ultimately culminate in the presentation of erythroderma/exfoliative dermatitis. Largely, it is a secondary process; therefore, it is mandatory to establish its etiopathology in order to facilitate its precise management. An increasing number of new drugs have been incriminated in the recent past. Its clinical pattern is fascinating and has been the subject of detailed studies. Its changing scenario in various age groups, its presentation postoperatively, and its occurrence in human immunodeficiency virus (HIV)-positive individuals are vivid indicators. Several factors may be responsible for the causation of this extensive skin disorder. Subtle/sudden generalization of pre-existing dermatoses may be an intriguing dilemma, and may reflect an individual variation. A detailed outline of a patient’s history to elicit possible triggering events, namely infections, drug ingestion, topical application of medications, sun/ultraviolet light exposure, and other factors, may be imperative. It is also challenging to manage the condition, because the intricate process puts an extensive strain on an already compromised body system. Furthermore, it is probable that the original dermatosis may be masked by extensive erythema/scaling, thus making it difficult to obtain a clear-cut diagnosis. This synopsis is an endeavor to revisit and update the information available on erythroderma/exfoliative dermatitis.

Definition

Erythroderma and exfoliative dermatitis are largely synonymous; however, erythroderma is the preferred term and is currently in vogue. Nonetheless, it is imperative to define these conditions. The former is characterized by extensive and pronounced erythema coupled with perceptible scaling, whereas the latter is conspicuous by the presence of widespread erythema and marked scaling. Accordingly, ≥90% skin surface involvement is considered as a salient prerequisite to make a clinical diagnosis of exfoliative dermatitis.

Incidence

It is hard to obtain a precise incidence for erythroderma/exfoliative dermatitis as most reports are retrospective, and do not address the issue of overall incidence. This aspect was dealt with for the first time by Sehgal and Srivastava in a large prospective study from the Indian subcontinent, where the incidence was recorded as 3.5 per 100,000 dermatologic outpatients. In another survey from The Netherlands, the annual incidence was recorded as 0.9 per 100,000 inhabitants. A study based on an analysis of 138 consecutive erythroderma patients from South Africa found that 75% were black, 22.5% Indian and 2.5% white. In addition, a large number of patients were HIV positive, and a drug reaction was the most common cause of erythroderma. Furthermore, males were affected 2–3 times more frequently, with an average male to female ratio of 2.3 : 1. In another study from Spain,
Psoriasis is the most common cause of exfoliative dermatitis amongst the dermatologic disorders, however, in children, psoriasis is the second most common cause of the disease, with drugs as the main culprit.

**Drugs**

Topical and systemic medications are notorious for precipitating erythroderma/exfoliative dermatitis. An apparent increase in the incidence of the disease may be directly proportional to the introduction of new drugs. Apart from the well-known allopathic medicines, homeopathic, unani, ayurvedic, herbal, and common home remedies have been incriminated. Many drug eruptions that commonly present as morbilliform, lichenoid, or urticarial forms may often progress to extensive erythema and exfoliation.

The inventory of drugs causing erythroderma/exfoliative dermatitis is increasing; however, the most common are shown in Table 2.

It is therefore pertinent to provide a inventory of drugs frequently responsible for causing such an episode.

Drug-induced erythroderma due to dapsone/antileprosy drug hypersensitivity may often mimic cutaneous T-cell lymphoma in terms of both clinical features and histopathology. Fortunately, it resolves after withdrawal of the offending drug(s) and the administration of supportive therapy.

**Malignancies**

Erythema/exfoliative dermatitis may ultimately be one of the clinical expressions of reticuloendothelial neoplasms and internal blood vessel malignancies. The latter invariably affect older individuals, and erythema/exfoliative dermatitis is considered to be a salient cutaneous marker of internal malignancy. Its incidence is around 1%. Lymphomas in general and T-cell lymphoma [comprising mycosis fungoides and Sezary syndrome (its leukemia variant, in particular)] are often reported to present as exfoliative dermatitis. They constitute over 25–45% of cases of malignancy-related erythrodermas. Exfoliative dermatitis may precede, accompany, or follow T-cell lymphomas, and its appearance may be identical to that of benign erythroderma.

An immunophenotypic study with the use of advanced antibody panels may be required to distinguish it from the benign form. Reticular cell sarcoma, acute and chronic leukemia, and malignant histiocytosis are a few other implicated conditions. Carcinoma of the colon, lung, prostate, thyroid, fallopian tubes, larynx, and esophagus have also been alleged to cause the condition.

**Miscellaneous/idiopathic disorders**

Hepatitis, irradiation, acquired immunodeficiency syndrome

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(AIDS), graft-vs.-host disease, Ofuji papuloerythroderma, and Omenn’s syndrome can also cause the condition.\textsuperscript{8,12,14,51,58–61} Despite the best endeavors, a small proportion of patients remain in whom no clear-cut etiology can be defined and these are classified under idiopathic disorders. Sustained efforts during the course of follow-up may lead to the precise definition of the etiology.\textsuperscript{8}

**Pathogenesis**

The pathogenesis of erythroderma/exfoliative dermatitis is unclear. Currently, it is believed that the condition is secondary to an intricate interaction of cytokines and cellular adhesion molecules, including interleukins-1, -2, and -8, intercellular adhesion molecule-1 (ICAM-1), and tumor necrosis factor (TNF).\textsuperscript{15} These interactions result in a dramatic increase in the epidermal turnover rate, causing a higher than normal mitotic rate and an increase in the absolute number of germinative skin cells. Furthermore, the time required for cells to mature and travel through the epidermis is decreased, and is manifested as an increased loss of epidermal material, together with a significant loss of protein and folate.\textsuperscript{62} In contrast, the exfoliation of normal epidermis is much less and contains very little important viable material, such as nucleic acids, soluble proteins, or amino acids.\textsuperscript{63}

Abel et al.\textsuperscript{26} studied the immunophenotypic characteristics of benign (psoriasis, dermatitis, drug-induced) and malignant (Sezary syndrome, mycosis fungoides) forms of erythroderma, and found them to be similar. In immunohistochemical studies conducted by Sigurdsson et al.,\textsuperscript{64,65} the dermal infiltrate in patients with Sezary syndrome mainly showed a T-helper-2 cytokine profile, while benign reactive erythroderma showed a T-helper-1 cytokine profile, indicating that, although clinically similar, they have different underlying pathogenic mechanisms.

**Clinical presentation**

Exfoliative dermatitis starts as patch(es) of erythema accompanied by pruritus. The patch(es) enlarge and coalesce to form extensive areas of erythema which eventually spread to cover whole/most of the skin surface. Exfoliative dermatitis is also associated with profuse scaling, which has its onset 2–6 days after erythema with individual variations.\textsuperscript{1,16,63} The acute form is heralded by the formation of large scales, whilst the chronic form is recognized by small scales.\textsuperscript{8} The skin is conspicuously bright red, dry, scaly, hot, and indurated (Fig. 1). Mild to severe pruritus is usually present. Lichen simplex chronicus may be its ultimate expression (Fig. 2). In addition, the nails become thick, lusterless, dry, brittle, and show ridging of the nail plate. Periorbital skin inflammation and edema cause ectropion and epiphora. Lymphadenopathy, hepatosplenomegaly, edema of the feet/ankles, and gynecomastia may also be observed. In black people, a widespread loss of pigmentation is usual. The basal metabolic rate is increased and a catabolic state causes significant weight loss over time.\textsuperscript{1} At times, patients can slip into an irreversible hypo- or hyperthermia. The former may result in ventricular bradycardia and hypotension. An increased peripheral blood flow may result in high-output cardiac failure. All body systems may be affected by these manifestations.\textsuperscript{8}

The general picture is modified accordingly to the nature of the underlying disorder, whose etiology and prompt treatment should be addressed. Generalized dermatitis usually occurs in the sixth or seventh decades of life; however, atopic dermatitis may occur at any age. Pruritus is at its worst in old age. Frenk et al.\textsuperscript{66} reported senile erythrodermic patches with increased serum immunoglobulin E (IgE) and lactic dehydrogenase levels together with eosinophilia.

Psoriasis is the most common underlying disorder, and its features may be present until the whole body develops exfoliative dermatitis. In a few cases, generalized pustular psoriasis may also be present. There may be a history of preceding plaque(s), treatment with tar, potent steroids, or psoralen

![Figure 1](image-url) Erythroderma/exfoliative dermatitis, whole of the skin surface was bright red, dry, scaly, hot and indurated
plus UVA (PUVA) therapy, intermittent infections, or emotional stress. A history of drugs for certain dermatoses/systemic disorders may be elicited prior to the onset of exfoliative dermatitis. Erythema is acute in onset and progresses to generalized exfoliation, which may resolve over the course of 2–6 weeks.

Erythroderma following pityriasis rubra pilaris is fairly diagnostic, as it usually starts in childhood or adulthood and the lesions occupy the hair follicle in the form of papules and/or plaques with “islands of sparing.”

Other uncommon causes are lichen planus, pemphigus foliaceus (Fig. 3), dermatophytosis, ichthyosiform erythroderma, crusted (Norwegian) scabies, graft-vs.-host disease, and irradiation. Postoperative erythroderma, a type of graft-vs.-host disease appearing several days after surgery along with blood transfusion, is characterized by erythroderma, fever, pancytopenia, hepatic insufficiency, and diarrhea, and may prove fatal. Exfoliative dermatitis may also develop during seroconversion in HIV-infected patients with florid manifestations.

Exfoliative dermatitis associated with lymphoma may show the classical features; however, it may fail to respond to corticosteroid therapy. It may continue to progress, even if repeated investigations over months or years fail to pinpoint any convincing etiology. Efforts should be continued to make a diagnosis as, sooner or later, lymphoma will be revealed. Sezary cells/immature neutrophils are diagnostic pointers. Hodgkin’s disease may also show unexplained eosinophilia.

### Hemodynamic/metabolic disturbances

The disease may cause an enormous aberration of body metabolism. The increased skin blood flow may cause hypothermia and profound heat loss. Compensatory hypermetabolism and an increased basal metabolic rate without any primary increase in thyroid activity may ensue. Excessive protein loss through scaling and leaking through skin, hemodilution due to the increased plasma volume, and hypermetabolism may contribute to hyperalbuminemia and severe edema. Furthermore, high-output cardiac failure may occur at any time.

### Histopathology

The histopathology of exfoliative dermatitis often reveals a nonspecific picture consisting of orthokeratosis (hyperkeratosis, parakeratosis), acanthosis, and a chronic perivascular inflammatory infiltrate with or without eosinophilia. Botella-Estradas et al. observed that the clinicopathologic correlation in erythroderma is difficult, because the specific features of the dermatosis are masked by the nonspecific features of
Table 3  Histologic clues to the diagnosis of erythroderma

<table>
<thead>
<tr>
<th>Disease</th>
<th>Histologic clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psoriasis</td>
<td>Parakeratosis, Munro’s microabscess, suprapapillary plate thinning, squinting papillae, regular acanthosis</td>
</tr>
<tr>
<td>CTCL/Sezary</td>
<td>Exocytosis of mononuclear cells, epidermotropism, Pautrier’s microabscesses</td>
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<tr>
<td>Drug reaction</td>
<td>Vascular change, necrotic keratinocytes</td>
</tr>
<tr>
<td>Actinic reticuloid</td>
<td>Hyperkeratosis, acanthosis, superficial and deep mixed dermal infiltrate with some atypical mononuclear cells</td>
</tr>
<tr>
<td>Pityriasis rubra pilaris</td>
<td>Alternating orthokeratosis and parakeratosis (vertically and horizontally) with or without keratotic plugging</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Dermal noncaseating epithelioid “naked” cell granulomas, occasional giant cells surrounded by sparse lymphocytes</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>Spongiosis, eosinophils within dermal infiltrate</td>
</tr>
<tr>
<td>Lymphoproliferative diseases</td>
<td>Interstitial pattern of atypical cells between collagen bundles</td>
</tr>
<tr>
<td>Scabies</td>
<td>Pervascular and interstitial infiltrates with eosinophils, scabetic mite/scybala in stratum corneum</td>
</tr>
<tr>
<td>Dermatophytosis</td>
<td>Focal parakeratosis, hyphae in stratum corneum</td>
</tr>
<tr>
<td>Pemphigus</td>
<td>Suprabasal intraepidermal cleavage, acantholytic keratinocytes (acantholytic cells), direct immunofluorescence depicting IgG bound to cell surface, circulating antibodies</td>
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<tr>
<td>Pemphigoid</td>
<td>Subepidermal bulla with eosinophils</td>
</tr>
<tr>
<td>Acute GVHD</td>
<td>Vacuolar change, satellite cell necrosis</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>Spongiosis, eosinophils within dermal infiltrate</td>
</tr>
<tr>
<td>Seborrheic dermatitis</td>
<td>Parakeratosis with neutrophils at lips of follicular ostia</td>
</tr>
<tr>
<td>Dermatomyositis/subcutaneous</td>
<td>Vacuum change, colloid bodies, increased dermal mucin</td>
</tr>
<tr>
<td>lupus erythematosus (SCLE)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic subacute</td>
<td>Parakeratosis, spongiosis, epidermal hyperplasia, papillary dermal edema, superficial perivascular lymphohistiocytic infiltrate</td>
</tr>
<tr>
<td>Idiopathic chronic</td>
<td>Compact hyperkeratosis, psoriasiform hyperplasia, little spongiosis, papillary dermal thickening</td>
</tr>
</tbody>
</table>

CTCL, cutaneous T-cell lymphoma; GVHD, graft-vs.-host disease; IgG, immunoglobulin G; SCLE, ?.

Erythroderma. In a study on Sezary syndrome, the diagnosis was established by the clonal population of T cells in the blood, despite a lack of diagnostic features on biopsy. Walsh et al. advocated that the submission of multiple simultaneous biopsies from the affected skin enhanced the accuracy of the histopathologic diagnosis, and the cause could be identified in up to one-half of cases. The stage of the disease can modify the histopathologic picture; in the acute stage, spongiosis and parakeratosis are prominent, whereas, in the chronic stage, acanthosis and elongated rete ridges are seen. Zip et al. reported that, despite the uniformity of the clinical expression of erythroderma, diagnostic histopathologic features of the underlying disease are retained in the majority of patients. Skin biopsies from characteristic clinical lesions may often confirm the diagnosis of psoriasis, pityriasis rubra pilaris, ichthyosiform erythroderma, or pemphigus foliaceus. Drug-induced exfoliative dermatitis may often reveal a lichenoid interface dermatosis histopathology. In erythroderma due to lymphoma, the infiltrate may gradually become polymorphic until it acquires specific diagnostic features. This makes repeated skin biopsies, additional investigations of lymphocytes in peripheral blood, and sustained follow-up in dubious situations mandatory to reveal the correct diagnosis.

Microscopic clues to the diagnosis of erythroderma, if reviewed systematically, can reveal the underlying diagnosis (Table 3). Additional tests to increase the diagnostic specificity include immunophenotyping and direct immunofluorescence.

Investigations/diagnosis

Mild anemia, leukocytosis, increased erythrocyte sedimentation rate, hypoalbuminemia, hyperglobulinemia, and hyperuricemia are frequent findings. Increased IgE may be observed in erythroderma when caused by atopic dermatitis and drug reactions, although it has also been reported in other settings. In a report by Griffiths et al., a decreased CD4 T-cell count was observed in patients with erythroderma in the absence of HIV disease, as a consequence of sequestration of the lymphocytes in the skin. Circulating Sezary cells at greater than 20% are indicative of Sezary syndrome, but at less than 10% are a nonspecific finding in erythroderma. Immunophenotyping, flow cytometry, and, in particular, B-cell and T-cell gene rearrangement analysis may be helpful in confirming the diagnosis of lymphoma when it is strongly suspected. Actinic retinoid is differentiated from Sezary syndrome by the increased CD8 T cells in the latter and the nuclear contour index of peripheral blood lymphocytes. A detailed guide to investigations is given in Table 4.
**Table 4 Investigations/laboratory tests**

**Basic investigations**
- Weight, temperature, pulse, respiratory rate charting
- Fluid intake/output charting
- Complete hemogram, total and differential leukocyte counts, absolute platelet count, erythrocyte sedimentation rate
- Liver and kidney function tests, including serum electrolytes
- Histopathology
- Scheduled urine macro- and microscopy
- Electrocardiogram (ECG) and chest radiograph
- Disease-specific investigations
- Skin scrapings/KOH (Norwegian scabies/extensive tinea corporis)
- Cultures may show bacterial overgrowth or the herpes simplex virus
- Angiotensin-converting enzyme levels, serum calcium (sarcoidosis)
- Serum and urine protein electrophoresis (multiple myeloma)
- 

**Disease-specific investigations**
- Immunology – antinuclear antibody, rheumatoid factor, anti-DNA
- Human immunodeficiency virus 1 and 2 testing, including Western blot
- Lysozyme/neutrophil elastase, serum albumin
- Electrocardiogram (ECG) and chest radiograph
- 

**Basic investigations**

A detailed history of the sequence of events leading to the development of erythroderma/exfoliative dermatitis is a prerequisite in all patients. Often the clues obtained may help in the diagnosis and appropriate management. A thorough clinical examination is required in order to diagnose the etiology of exfoliative dermatitis and to allow appropriate urgent symptomatic treatment. An astute practitioner will be able to identify the nature of the underlying dermatosis, and proceed to confirm his or her suspicions.

Histopathology is paramount and is rewarding in over 50% of cases if a diligent effort is made. Fine needle aspiration cytology (FNAC) may be vital to distinguish between dermatopathic lymphadenopathy and malignant lymphadenopathy.

In a recent development, Charry et al. concluded that heteroduplex analysis of T-cell receptor gamma gene rearrangement can be used as an important diagnostic tool in skin biopsies to classify the underlying etiology of erythroderma.

### Management

All cases should be considered as a dermatologic emergency and should preferably be hospitalized for treatment. Serious general medical problems may occur in due course if not appropriately treated. The initial management of all types of erythroderma is the same regardless of the etiology. The principle of management is to maintain skin moisture, avoid scratching, avoid precipitating factors, apply topical steroids, and treat the underlying cause and complications. Together with general management, all unnecessary medication should be avoided. Cutaneous applications should be soothing and mild due to the already inflamed skin. Mild topical steroids/emollients after lukewarm washing can act as an antipruritic. Antihistamines (H1 receptor) can be administered to enhance the effect. Once the acute irritated state of the skin has improved, further treatment can be undertaken according to the etiology. Antimicrobials can be added to control secondary infections. Any hemodynamic or metabolic aberrations must be addressed appropriately. Each case requires regular monitoring of protein, electrolyte balance, circulatory status, and body temperature. Blood urea, serum electrolyte, and fluid balance should be monitored.

Erythroderma commonly resists therapy until the underlying disease is treated (e.g., phototherapy, systemic medications in psoriasis). The outcome is unpredictable in idiopathic erythroderma and the course is marked by multiple exacerbations; prolonged glucocorticoid therapy is often needed. Appropriate inpatient/outpatient medications are influenced by the underlying etiology of erythroderma. For example, prednisone may be contraindicated in exfoliative dermatitis secondary to psoriasis, whereas retinoids are an excellent choice for this disease. Systemic steroids may be helpful in some cases, but should be avoided in suspected cases of psoriasis and staphylococcal scalded skin syndrome. Low-dose methotrexate or cyclosporine can be safely administered in erythrodermic psoriasis. Smith and Skelton found carbamazepine to be effective in the treatment of psoriatic erythroderma; however, the same drug has caused exfoliative dermatitis/erythroderma in a few studies. Similarly, methotrexate therapy for psoriasis has been reported to cause exfoliative dermatitis. The ideal treatment for erythrodermic cutaneous lymphoma is still elusive. Various modalities, such as systemic steroids, PUVA, total body electron-beam irradiation, topicals nitro mustard, systemic chemotherapy, and extracorporeal plasmapheresis, have been tried with variable results. A proposed plan of treatment is given in Table 5.

### Complications and prognosis

Exfoliative dermatitis is a complex disorder involving many factors, but the net outcome depends on the underlying disease. The disease course is rapid if it results from drug allergy, lymphoma, leukemia, contact allergens, or staphylococcal scalded skin syndrome. The disease course is gradual if it...
results from the generalized spread of a primary skin disease (e.g. psoriasis, atopic dermatitis).\textsuperscript{11,16,17} Drug-induced cases of exfoliative dermatitis recover completely if initial medical management is promptly undertaken.\textsuperscript{4}

Despite skilled efforts, exfoliative dermatitis can sometimes prove fatal, especially in elderly patients. Secondary infection, dehydration, electrolyte imbalance, temperature dysregulation, and high-output cardiac failure are potential complications in all cases.\textsuperscript{11,55} Postinflammatory hypopigmentation or hyperpigmentation may occur, especially in individuals with dark skin.\textsuperscript{11} Generalized vitiligo or pyogenic granuloma have also been recorded after exfoliative dermatitis.\textsuperscript{35,57} Nevi and keloid formation are rare benign sequelae, as are alopecia and nail dystrophies.\textsuperscript{3} In initial documented studies, the recorded death rate varied from 18 to 64\%;\textsuperscript{1,6,48–50} however, the mortality has been reduced due to advances in diagnosis and therapy.

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Education

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Education

Erythroderma/exfoliative dermatitis


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