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The rash that becomes an erythroderma

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Abstract Erythroderma is a dermatologic emergency with potentially serious consequences. Several diseases with different etiologies characteristically appear as erythroderma. Depending on the age groups, congenital ichthyosiform disorders, infections, preexisting dermatoses, drug eruptions, and internal malignancies commonly present with, or progress to, erythroderma. The course, prognosis, and management strategies also vary depending on the cause of erythroderma; hence, an accurate diagnosis is essential in minimizing associated morbidity and mortality. The generalized erythema and scaling often obscure the classic clinical features of the underlying skin diseases, posing a diagnostic challenge to dermatologists. Awareness and elicitation of subtle signs and clinical manifestations are crucial. A step-wise approach ensures completeness of clinical evaluation and avoids missing any relevant clinical data. The initial clinical presentation, cutaneous examination findings, and systemic clues reveal important information regarding the diagnosis, course, and prognosis of erythroderma. The age at onset, symptomatology, duration of illness, initial lesions, initial site of onset, clinical course, family history, types of scales, changes in cutaneous integuments and systemic clues will assist in delineating the nature of underlying disease.

Introduction

Erythroderma is an extreme state of anatomic and physiologic dysfunction of skin, characterized by extensive erythema and scaling involving more than 90% of body surface area. Neonatal and infantile erythroderma are very rare, and their frequency is not known. An Indian study showed incidence in 20 out of 19,000 pediatric patients (0.11%) attending a dermatology unit.[1] The annual incidence of erythroderma in adults varies geographically, ranging from 0.9 cases per 100,000 persons in the Netherlands to 1-2 cases per 100,000 persons in Finland. The hospital incidence has been reported as 4.9 cases per year in Thailand, to 35 cases per 100,000 patients with dermatologic conditions in India, and 30-44 cases per 100,000 patients with dermatologic conditions in Tunisia.[2]

Overall, the patients presenting with erythroderma usually are men; however, gender distribution in different etiologies has been reported to be the same.[3] Various diseases with different etiopathologic processes can present as or progress to erythroderma (Table 1). It is associated with significant morbidity and mortality in addition to the variable prognosis inherent to the underlying etiology.

The precise diagnosis of erythroderma is essential for proper management and better therapeutic outcome; hence, a step-wise clinical approach is described to reveal the evolution of a rash into erythroderma. The diseases presenting as, and those with a tendency to develop erythroderma, are many. The diseases presenting with predominantly vesiculobullous

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Table 1 Etiopathogenesis list of diseases causing erythroderma

- ○ Inflammation
  - ▪ Psoriasis
  - ▪ Pityriasis rubra pilaris
  - ▪ Lichen planus
  - ▪ Eczemas
- ○ Infection and Infestation
  - ▪ Staphylococcal scalded skin syndrome
  - ▪ Toxic shock syndrome
  - ▪ Congenital cutaneous candidosis
  - ▪ Dermatophytoses
  - ▪ Crusted scabies
- ○ Infiltration
  - ▪ Sézary syndrome
  - ▪ Mycosis fungoides
  - ▪ Diffuse cutaneous mastocytosis
  - ▪ Internal malignancy
- ○ Ingestion
  - ▪ Drugs
  - ▪ Alternative medicines
  - ▪ Systemic contact dermatitis
- ○ Inherited
  - ▪ Ichthyosiform disorders
  - ▪ Primary immunodeficiency disorders
  - ▪ Metabolic disorders
- ○ Immunologic
  - ▪ Graft-versus-host disease
  - ▪ Dermatomyositis
  - ▪ Subacute cutaneous lupus erythematosus
  - ▪ Sarcoidosis
- ○ Idiopathic

Table 2 Age list of common diseases causing erythroderma

- ○ Neonates and Infants
  - ▪ Congenital
    - ● Nonsyndromic congenital ichthyosis
    - ● Syndromic congenital ichthyosis
    - ● Omenn syndrome and graft-versus-host disease
    - ● Congenital cutaneous candidosis
    - ● Psoriasis
    - ● Diffuse cutaneous mastocytosis
    - ● Staphylococcal scalded skin syndrome
  - ▪ Noncongenital
    - ● Psoriasis
    - ● Eczemas: Atopic dermatitis
    - ● Seborrheic dermatitis
    - ● Staphylococcal scalded skin syndrome
    - ● Drugs: Vancomycin and ceftriaxone
    - ● Metabolic disorders:
      - ○ Holocarboxylases synthetase and biotinidase deficiency
      - ○ Essential fatty acid deficiency
- ○ Childhood (Preschool and School-Age)
  - ▪ Infections
    - ● Staphylococcal scalded skin syndrome
    - ● Crusted scabies
  - ▪ Drugs: Antiepileptics, amoxicillin, sulfonamides, antitubercular drugs
  - ▪ Eczemas: Atopic dermatitis
  - ▪ Psoriasis
- ○ Adults
  - ▪ Preexisting dermatoses: Psoriasis, contact dermatitis, airborne contact dermatitis, chronic actinic dermatitis atopic dermatitis
  - ▪ Drugs: Antiepileptics, antimicrobials, analgesics
  - ▪ Cutaneous T cell lymphomas: Sézary syndrome, mycosis fungoides
  - ▪ Internal malignancies
  - ▪ Multisystem disorders: Dermatomyositis, subacute cutaneous lupus erythematosus
  - ▪ Idiopathic

lesions, and those with a transient, self-limiting and benign course, such as transient neonatal skin diseases and viral exanthema, are excluded.

Clinical approach

The clinical homogeneity of generalized erythema and scaling often obscure classic clinical features of underlying dermatoses posing a diagnostic challenge for dermatologists. In neonates, identifying the underlying cause for erythroderma is quite difficult due to overlapping clinical features and hesitancy in subjecting newborns to an array of invasive investigations. It leads to delay in diagnosis by 3 to 11 months, and, in 10% of cases, the diagnosis remains unconfirmed even after 3 to 5 years.[4] The main objective of effective and efficient clinical approach to any disorder is chronologic elicitation of signs and symptoms through history taking and clinical examination. A step-wise approach ensures completeness of clinical evaluation and avoids missing any relevant clinical data. Detailed history usually reveals preexisting dermatoses and predisposing factors that are responsible for generalized spread, leading to erythroderma. Thorough clinical examination, focusing on subtle clinical clues and tests helps in the differential diagnosis. The erythroderma, irrespective of underlying causes, culminates in a state of acute skin failure, characterized by loss of barrier and metabolic functions; hence, the clinical inquiry should also extend to identify the local or systemic complications of erythroderma. The interpretation of documented clinical data provides important information on diagnosis, etiologic and predisposing factors, systemic associations, complications, prognosis, management strategy, and monitoring of course of the disease.

Clinical presentation

Patients with erythroderma present to dermatologists with varied clinical presentations. They differ in age at onset, duration of illness, symptomatology, mode of onset, initial site of involvement, initial lesion, clinical course of disease, predisposing factors, and family history. The detailed evaluation of

Table 3 Initial site of involvement in diseases progressing to erythroderma

Sl no	Disease	Initial site of involvement
1	Staphylococcus scalded skin syndrome	Face and flexural folds
2	Pityriasis rubra pilaris	Scalp and face
3	Airborne contact dermatitis	Eyelids, retroauricular area, and nasolabial folds
4	Holocarboxylase synthetase deficiency	Periorificial areas
5	Essential fatty acid deficiency	Intertriginous regions
6	Psoriatic erythroderma in neonates and infants	Diaper area
7	Pemphigus foliaceous	Seborrheic area

clinical presentation helps in understanding the nature and severity of underlying etiology.

Age at onset

Erythroderma can affect all age groups from neonates to the elderly. The prevalence of underlying causes for erythroderma varies across the spectrum of age (Table 2). Infants with erythroderma usually present before the age of 4 months. Erythroderma at birth, also known as congenital erythroderma, is caused by congenital ichthyosiform erythroderma (CIE), primary immunodeficiency, and Netherton syndrome.[4] Holocarboxylase synthetase deficiency manifests clinically at birth or neonatal period. Biotinidase deficiency presents in early infancy at 3 months of age.[5] Atopic dermatitis (AD) and seborrheic dermatitis develop at 6 to 8 weeks of life. Psoriatic erythroderma, though rare, may occur in early infancy. Congenital cutaneous candidosis (CCC) may appear during the first week of life.[4] Drug-induced erythroderma is common in children.[2]

In adults, preexisting dermatoses are the predominant cause of erythroderma, with psoriasis being the most common among them.[6] Internal malignancies, which may present as erythroderma, are reticuloendothelial, solid organ, and blood vessel malignancies. Multisystem disorders, including dermatomyositis, systemic lupus erythematosus, and sarcoidosis, may rarely present with erythroderma.[7] Erythroderma of unknown etiology is common in patients older than 60 years.[3]

Duration of illness

Duration of disease is shortest with a drug-induced etiology. In the absence of preexisting dermatoses, a longer duration from the onset of the disease has been reported with cutaneous T cell lymphoma (CTCL) and internal malignancy.[7]

Symptoms

The associated symptoms may be variable as they depend on the underlying cause. Generally, some grade of itching is expected in erythroderma due to generalized dry scales and tightness of skin. Irritant contact dermatitis is associated with pain and a burning sensation. The patients with allergic contact dermatitis, chronic actinic dermatitis, crusted scabies, lichen planus, and Sézary syndrome often present with severe itching.[6] Severe pruritus is characteristically seen in Omenn syndrome; however, the ability to scratch develops in infants only after 3 months.[5] Moderate to severe itching is present in thymoma associated multiple organ disease.[8] Patients with

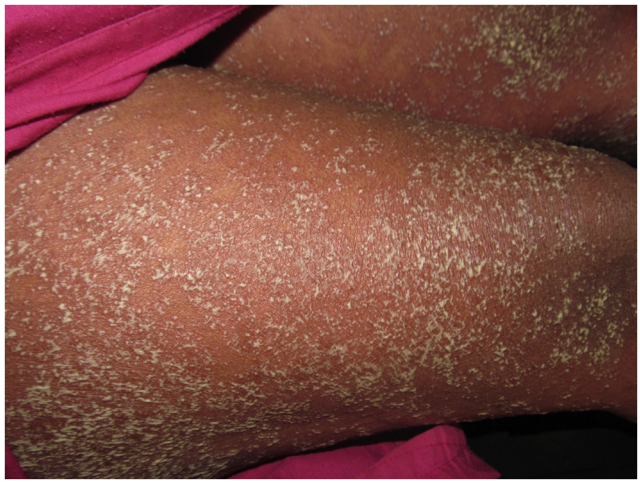

Fig. 1 Diffuse erythema with pustules characteristic of pustular psoriasis.

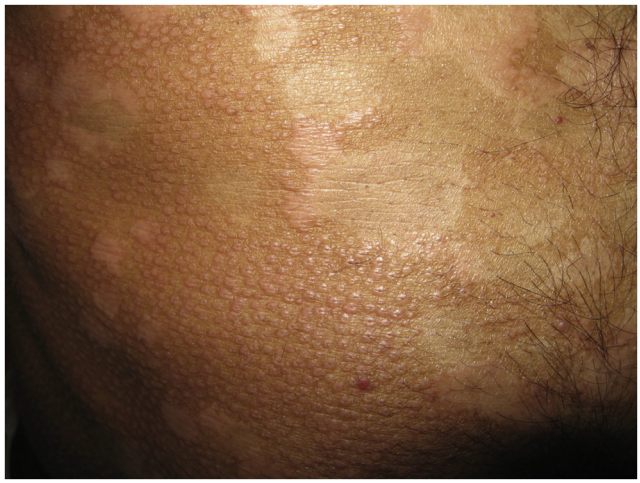

Fig. 2 Erythematous follicular papules with tendency to coalesce and islands of sparing in pityriasis rubra pilaris.

Table 4 Morphologic list of diseases progressing to erythroderma

- Erythema
  - Vancomycin-induced erythroderma
  - Staphylococcus scalded skin syndrome
  - Diffuse cutaneous mastocytosis
- Morbiliform
  - Graft-versus-host disease
  - Congenital cutaneous candidosis
  - Drug hypersensitivity syndrome
- Papules and plaques
  - Nonfollicular
    - Psoriasis
    - Lichen planus
    - Subacute lupus erythematosus
    - Dermatophytoses
    - Crusted scabies
    - Mycosis fungoides
  - Follicular
    - Pityriasis rubra pilaris
    - Follicular psoriasis
- Pustular
  - Pustular psoriasis
  - Acute generalized exanthematous pustular eruption
  - Congenital cutaneous candidosis (scattered)
  - Pemphigus foliaceous
  - Drug hypersensitivity syndrome
- Vesicular/erosive
  - Bullous congenital ichthyosiform erythroderma
  - Pemphigus foliaceous
  - Staphylococcal scalded skin syndrome
  - Diffuse cutaneous mastocytosis
  - Congenital cutaneous candidosis (scattered)
  - Essential fatty acid deficiency (Intertriginous)
- Eczematous
  - Atopic dermatitis
  - Seborrheic dermatitis
  - Sézary syndrome
  - Contact dermatitis
  - Holocarboxylase and biotinidase deficiency
  - Essential fatty acid deficiency
- Collodion membrane
  - Harlequin ichthyosis
  - Nonbullous ichthyosiform erythroderma
  - Lamellar ichthyosis
  - Pleomorphic ichthyosis
  - Netherton syndrome
  - Sjögren-Larsson syndrome
  - Conradi-Hunerman-Happle syndrome
- Ichthyosiform
  - Diseases presenting with collodion membrane
  - Bullous congenital ichthyosiform erythroderma

vesiculobullous diseases, such as pemphigus foliaceous and staphylococcal scalded skin syndrome (SSSS), may present with pain. Skin tenderness is characteristically present in SSSS, leading to a baby crying when held. Fever is associated with drug hypersensitivity syndrome (DHS), maternal-fetal graft-versus-host disease (GVHD), SSSS, or complications, such as secondary bacterial infection.[6] Low-grade fever and weight loss can be seen in TAMA.[8] Fever associated with appearance of new crops of pustules is characteristic of acute generalized pustular psoriasis. The association of fever, fatigue, gastrointestinal symptoms, and myalgia indicates increased levels of cytokines. This paradoxical reaction resulting in exacerbation of underlying psoriasis has been reported in patients receiving antitumor necrosis factor alpha drugs.[9]

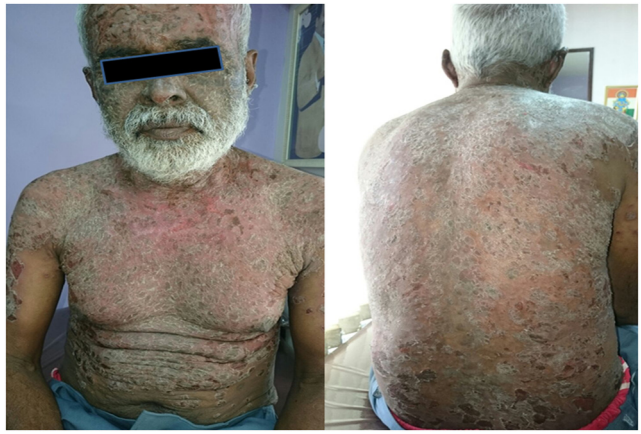

Fig. 3 Scale-crusts with a few erosion in pemphigus foliaceus. Reproduced with permission from Dr. Sharad Mutalik, Pune, India.

Mode of onset

The initial clinical presentation can be varied, depending on the underlying cause. Drug-induced erythroderma presents as a sudden onset of skin lesions. The acute exacerbation of primary cutaneous disorders can also present as sudden onset of skin lesions with the background of characteristic chronic skin lesions. Such a scenario warrants a look into possible predisposing factors. The onset and progression of the lesions is gradual in erythroderma secondary to primary cutaneous disorders.[6]

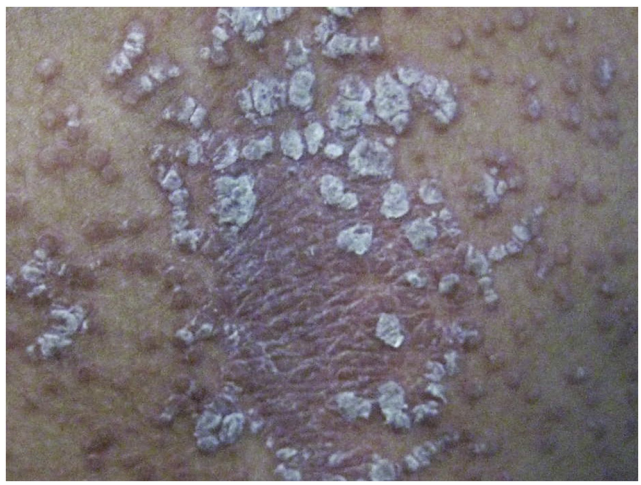

Fig. 4 Branlike or small husklike scales with characteristic follicular papules in pityriasis rubra pilaris.

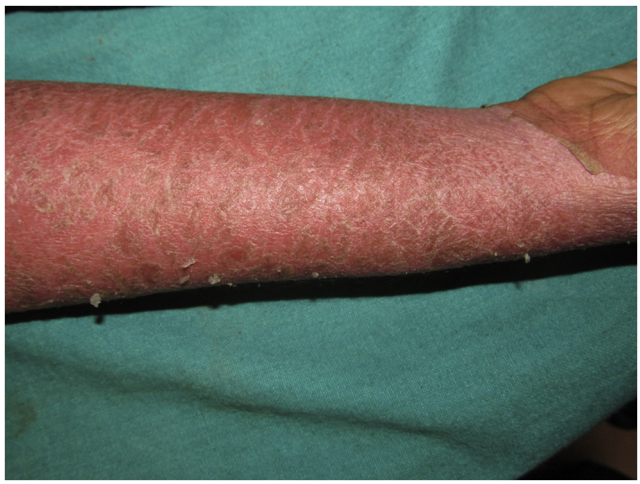

Fig. 5 Erythema with white large scales in acute generalized pustular psoriasis.

Initial site of involvement

Certain diseases characteristically affect a particular site at the onset of the illness (Table 3). It gives an important clue in the differential diagnosis.

Fig. 6 Large, brown, platelike scales with mild erythema and alopecia in lamellar ichthyosis.

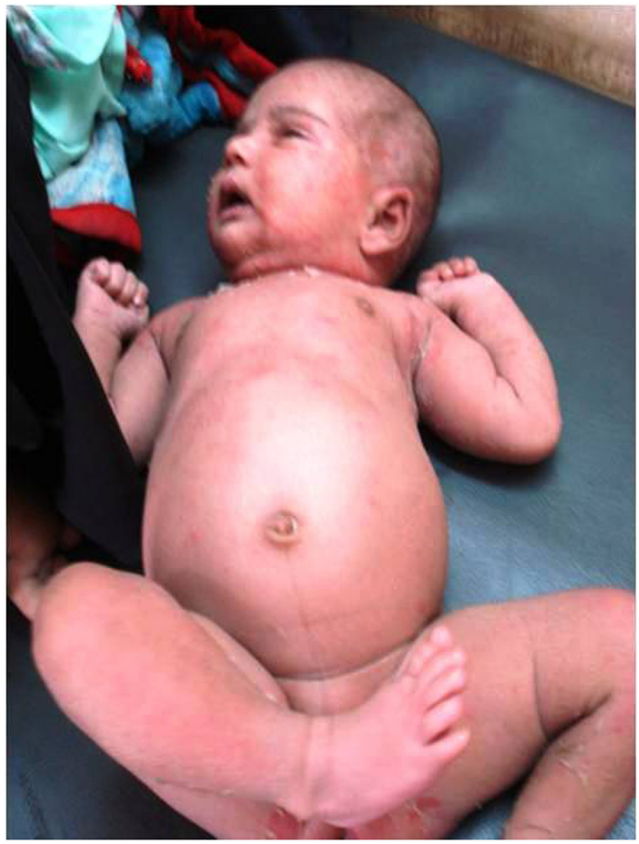

Fig. 7 Diffuse erythema and desquamation in staphylococcal scalded skin syndrome. Erythema is not readily appreciated due to the darker skin color.

Fig. 8 Cornflake skin in pemphigus foliaceous.

Table 5 Type of scales in different diseases causing erythroderma

Sl no	Type of scale	Disease
1	Corn flakelike (Figure 8), scale-crusts	Pemphigus foliaceous
2	Branlike, yellow greasy scales	Seborrheic dermatitis
3	Fine scales	Atopic dermatitis, dermatophytoses
4	Double-edged scales (ichthyosis linearis circumplexa)	Netherton syndrome
5	Large, dark, platelike scales	Lamellar ichthyosis
6	Fine, feathery scales	Nonbullous congenital ichthyosiform erythroderma
7	Perioral scale-crusts	Staphylococcal scalded skin syndrome
8	Hyperkeratotic crusts	Crusted scabies
9	Collaret scales	Congenital cutaneous candidosis
10	Branlike or small husklike dry scales (furfuraceous)	Pityriasis rubra pilaris
11	Desquamation	Staphylococcal scalded skin syndrome, Acute generalized exanthematous pustular eruption

Initial lesions

The clinical state of erythroderma usually evolves from the localized appearance of one or more primary lesions unique to underlying etiology (Figures 1 and 2; Table 4). Nonbullous congenital ichthyosiform erythroderma (NBCIE) and lamellar ichthyosis may present as a collodion baby at birth. After the shedding of the collodion membrane at around 3 weeks of age, erythema and scaling that cover the entire body are revealed in NBCIE.[10] DHS initially presents with morbiliform, lichenoid, pustular, or urticarial lesions. Erythematous annular or polycyclic scaly plaques are typically seen in subacute cutaneous lupus erythematosus.[11]

Clinical course

The speed and pattern of how lesions spread, response to treatment, and history of recurrence help in the differential diagnosis of erythroderma. The progression of erythroderma depends on underlying disease. Erythroderma due to DHS, contact allergy, CTCL, leukemia, and SSSS show faster progression, whereas a slower progression is characteristic of primary cutaneous disorders like psoriasis and AD.[7] The pattern of progression of disease is unique in pityriasis rubra pilaris and CCC. The former show typical cephalocaudal progression and in the latter, the rash spreads from the truncal to acral areas, including the palms and soles.[4] In erythroderma due to infectious causes, generalized erythema and scaling occurs during the subsiding phase of the disease.[1]

Drug-induced erythrodermas usually do not relapse, unlike those due to other causes. On the contrary, psoriatic erythroderma is known for recurrences. Resolution of the disease is faster in drug-induced erythroderma. Idiopathic erythroderma should be closely monitored, as some of these patients may evolve into CTCL. Others may be categorized into senile AD and drug-induced erythroderma. In the latter, there is a possibility that the patient has forgotten the drugs they took, or it may be neglected by the physician during the evaluation of erythroderma.[2] In adults, progressive worsening and refractoriness to treatment indicate the possibility of internal malignancy.[7]

Table 6 Diseases causing erythroderma involving palms and soles

- Congenital ichthyosiform erythroderma
- Omenn syndrome
- Congenital cutaneous candidosis
- Psoriasis
- Pityriasis rubra pilaris
- Sézary syndrome
- Crusted scabies

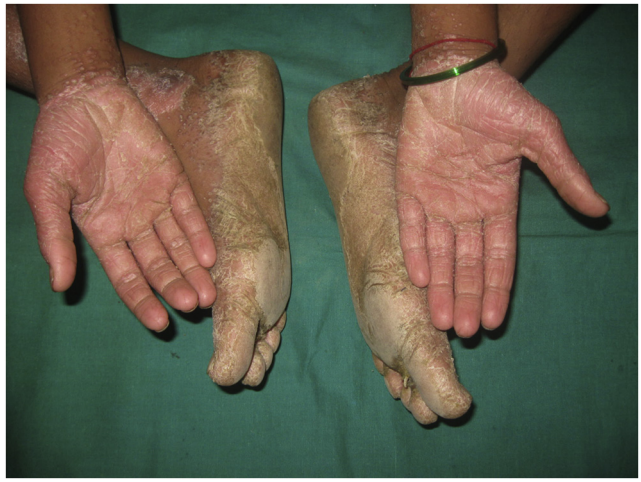

Fig. 9 Palmoplantar keratoderma with keratodermic sandal in pityriasis rubra pilaris.

Predisposing factors

Occupational, recreational, traditional, or therapeutic exposure to irritants or contact allergens support the diagnosis of erythroderma due to contact dermatitis. It is a common practice in India to apply a paste of Neem leaves or various other native medications for any exanthematous condition that predisposes to erythroderma. Seasonal exacerbation and aggravation of disease on sun exposure indicate airborne contact dermatitis and chronic actinic dermatitis, respectively. HIV infection is known to increase the risk of drug-induced erythroderma.

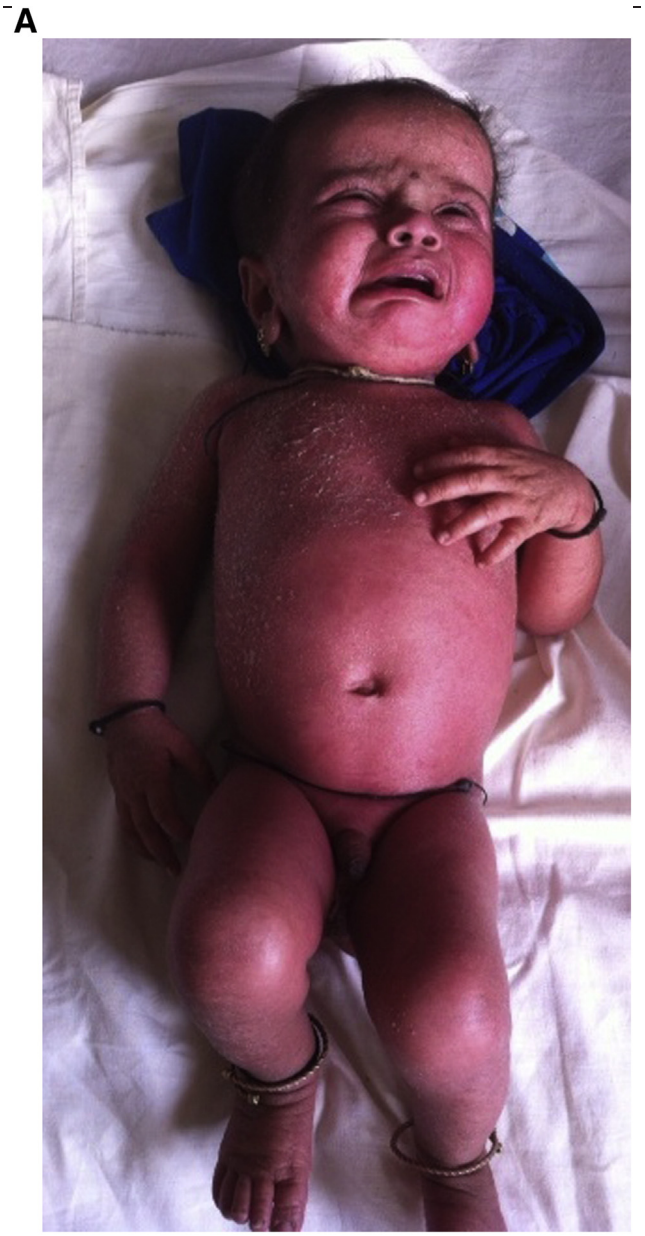

Fig. 10 Nonbullous congenital ichthyosiform erythroderma and scarring alopecia in nonbullous congenital ichthyosiform erythroderma.

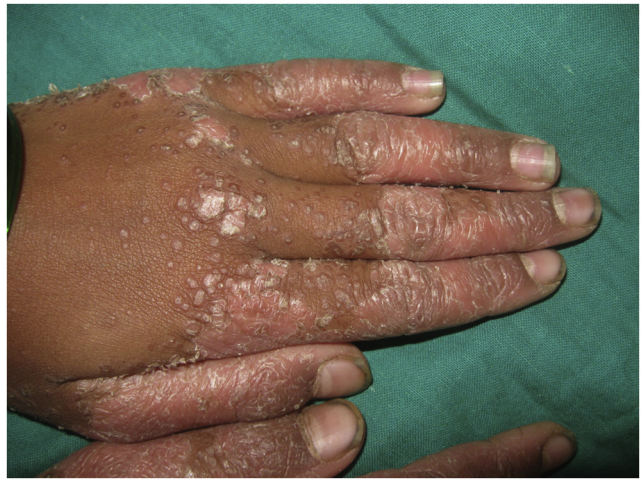

Fig. 11 Black dots or follicular keratotic papules on the proximal phalanx diagnostic of pityriasis rubra pilaris.

Antiepileptics and drugs used in upper respiratory tract infections are common culprits in drug-induced erythroderma in children. A history of transplacental–maternal–fetal transfusion in neonates indicates possibility of GVHD, especially in the presence of T cell immunodeficiency. Premature infants with CCC are at increased risk of invasive systemic infections leading to respiratory distress.[4] A history of parenteral nutrition may lead to nutritional deficiencies like essential fatty acid deficiency,[1] whereas a history of intrauterine device implantation in the mother and white macules on the placenta and umbilical cord may be present in a newborn with CCC.[5] In case of crusted scabies, an enquiry should be made regarding immunosuppression either due to drugs or HIV and human T-lymphotropic virus infection; severe systemic diseases like leprosy, systemic lupus erythematosus, rheumatoid arthritis, or leukemia; and conditions leading to the inability to scratch like mental illness, paresis, sensory neuropathy, or senility.[12]

Family history

In neonates and infants with psoriatic erythroderma, the family history is highly positive. A family history of atopy helps in the diagnosis of AD. Family pedigree helps in inherited disorders like CIE, primary immunodeficiency disorders, and metabolic diseases.[4] There may be the presence of an epidermal nevus with epidermolytic hyperkeratosis in parents of patients with NBCIE.[13] Unexplained death of siblings indicates primary immunodeficiencies like Omenn syndrome and Netherton syndrome.[14] Elicitation of a history of drug hypersensitivity in the family not only assists in the diagnosis of DHS but also is essential in choosing an appropriate drug in the management of erythroderma.

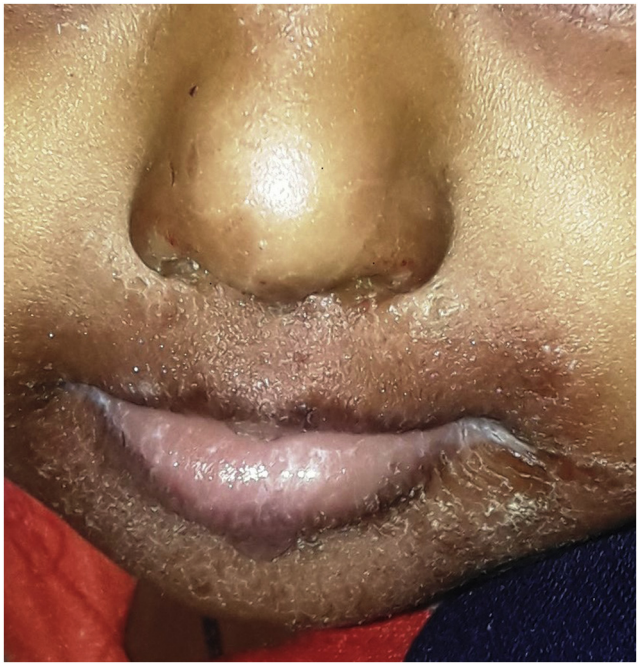

Fig. 12 Perioral radiating scale-crusts diagnostic of staphylococcal scalded skin syndrome.

Clinical examination

During the evolution of erythroderma from preexisting dermatoses, the classic lesions of underlying dermatoses are evident in making the diagnosis quite obvious; however, a fully developed erythroderma, irrespective of underlying cause, is clinically characterized by generalized erythema and scaling. In such a presentation, thorough examination of the skin and its integument is crucial for recognizing subtle clinical features that act as diagnostic clues.

Cutaneous examination

Erythema, scaling, and induration are the fundamental cutaneous examination findings in erythroderma. The description of each aids in eliciting the underlying cause of erythroderma.

Erythema

The hue of erythema can be prominent in some dermatoses causing erythroderma. These colors are described and appreciated in the background of white colored skin; hence, due consideration should be given to the color of the skin when interpreting a hue of erythema. Salmon-colored or orange-red erythema in pityriasis rubra pilaris, deep purple-red in CTCL, melano-erythroderma in paraneoplastic erythroderma, and red-brown papules in papulo-erythroderma of Ofuji have been described in literature.[15]

Scaling

The nature of scaling indicates the stage of erythroderma. The larger and crusted scales are seen in the acute phase, whereas in the chronic phase smaller and dry scales are seen. The type of scales sometimes indicates the underlying cause (Figures 3-8; Table 5).

Induration

Erythroderma can be diffuse or localized to a particular area. Erythroderma with induration of skin is characteristic of primary immunodeficiency disorders like Omenn syndrome.[14] Diffuse infiltration of the skin is also seen in Sézary syndrome.[15] In pre-existing dermatoses, the thickening of classic sites of involvement is evident. Flexural areas are lichenified in AD, and extensor surface of extremities are thickened in psoriasis.

Palms and soles

The involvement of palms and soles is characteristically present in several disorders causing erythroderma (Table 6). Palmoplantar keratoderma is more prominent in NBCIE among CIE disorders. Hyperkeratotic crusts on the palms and soles indicate crusted scabies. Palmoplantar keratoderma in pityriasis rubra pilaris has been described characteristically as "keratodermic sandal" with yellow tinge (Figure 9). In CCC, erythema typically involves palms and soles.[15]

Hair

Examination of scalp hair gives important clues to the diagnosis in neonatal and infantile erythroderma. Alopecia, a common feature of CIE, may be present in half of the infants with AD. Sparse hair and bamboo hairs are characteristic of Netherton syndrome. The latter may not be present until 10 months of age.[4] Scarring alopecia is seen in NBCIE (Figure 10), patchy alopecia is seen in biotinidase deficiency,[5] and severe alopecia is seen in Omenn syndrome.[14] Progressive alopecia is also seen in biotin and essential fatty acid deficiency.[1] Hypertrichosis affecting dorsum of hands is characteristic of reticular ichthyosis.[16]

Nail

The nail changes of preexisting dermatoses are evident in patients with erythroderma due to a slower growth rate of nails.[15] Onycholysis, with subsequent complete shedding of the nail plate, indicates an acute erythrodermic process.[17] The nail changes seen in patients with erythroderma include discoloration, brittleness, dullness, subungual hyperkeratosis, Beau lines, paronychia, and splinter hemorrhages.[15] In neonates and infants, onychodystrophy is seen in NBCIE

Table 7 Cutaneous examination clues for the diagnosis of diseases causing erythroderma[15,18]

Sl no	Cutaneous examination clues	Disease
1	Preexisting plaques, involvement of periumbilical area (infants), typical nail changes	Psoriasis
2	Preexisting eczematous/lichenified flexural lesions, prurigo, sparing of diaper area (infants)	Atopic dermatitis
3	Black dots or follicular hyperkeratotic papules on proximal phalanx of fingers, islands of sparing of skin	Pityriasis rubra pilaris
	Annular and polycyclic erythematous plaques	Subacute cutaneous lupus erythematosus, dermatophytosis
4	Facial edema, purpuric rash on dependent areas	Drug reactions
5	Sparing of skin folds (deck-chair sign) in elderly men	Papuloerythroderma of Ofuji
6	Macerated and malodorous intertriginous area, positive Nikolsky sign	Pemphigus foliaceous
7	Tenderness of skin, perioral radiating scale-crusts, positive Nikolsky sign	Staphylococcal scalded skin syndrome
8	Linear and swirled pattern of hyperkeratosis/hyperpigmentation	Conradi-Hunerman-Happle syndrome
9	Scalp involvement with or without alopecia	Omenn syndrome
10	Erythema without scaling, Darier sign, doughy skin, flushing	Diffuse cutaneous mastocytosis
11	Marked periorificial eczematous lesions	Holocarboxylase synthetase deficiency
12	Multiple confettilike normal skin	Reticulate ichthyosiform erythroderma (ichthyosis with confetti)[16]
13	Leonine facies	Cutaneous T cell lymphoma, chronic actinic dermatitis
13	Heliotrope rash, Gottron papules/sign, poikiloderma	Dermatomyositis

Table 8 General physical and systemic examination clues[15,18]

Sl no	Systemic examination clues	Diseases and complications
1	Lethargy	Holocarboxylase deficiency, severe dehydration
2	Irritability	SSSS, dehydration
3	Failure to thrive	Netherton syndrome, GVHD, Omenn syndrome, psoriasis in children
4	Loss of weight	Malignancy, chronic erythroderma
5	Pallor (Anemia)	GVHD, chronic erythroderma
6	Lymphadenopathy	Omenn syndrome, dermopathic lymphadenopathy, Sézary syndrome
7	Icterus	GVHD
8	Pedal edema	DHS, hypoproteinemia
9	Cold and calmly extremities	Hypovolemic or septic shock
10	Decreased sweating	CIE (especially pleomorphic ichthyosis (PI))
11	Fever	Drug hypersensitivity, SSSS, toxic shock syndrome, GVHD, acute generalized pustular psoriasis, sepsis
12	Hypotension	SSSS, toxic shock syndrome, vancomycin induced erythroderma, severe dehydration, sepsis
13	Hepatosplenomegaly	Omenn syndrome
14	Diarrhea	Omenn syndrome, diffuse cutaneous mastocytosis, GVHD
15	Recurrent infections/pneumonia	Netherton syndrome, Omenn syndrome, biotin deficiency, atopic dermatitis
16	Hypernatremic dehydration	Netherton syndrome, Omenn syndrome, Increased TEWL in neonates and infants
17	Dehydration	Holocarboxylase deficiency, increased TEWL
18	Cardiac failure	Complication of erythroderma in elderly
19	Seizures	Sjögren-Larsson syndrome, biotinidase deficiency, severe dehydration
20	Spastic diplegia/tetraplegia, psychomotor delay	Sjögren-Larsson syndrome
21	Severe ketoacidosis, metabolic coma, hyperammonemia, hypoglycemia	Holocarboxylase synthetase deficiency
22	Ectropion, eclabium	NBCIE, lamellar ichthyosis, PI, harlequin ichthyosis (HI)
23	Cataract	Conradi-Hunerman-Happle syndrome
24	Glistening dots (crystalline deposits) on fundoscopy	Sjögren-Larsson syndrome

CIE, congenital ichthyosiform erythroderma; DHS, drug hypersensitivity syndrome; GVHD, graft-versus-host disease; NBCIE, Nonbullous congenital ichthyosiform erythroderma; SSSS, staphylococcal scalded skin syndrome; TEWL, transepidermal water loss.

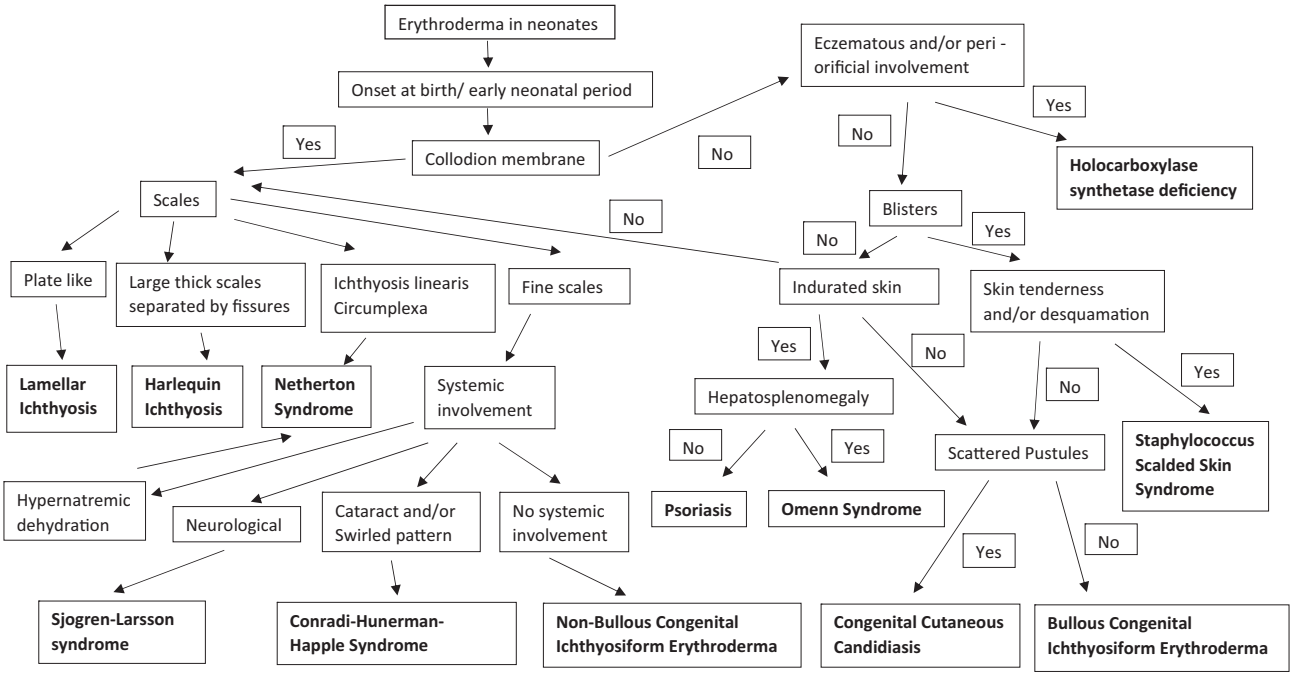

Fig 13 An algorithmic approach to differential diagnosis of erythroderma presenting at birth or in the early neonatal period.

and Omenn syndrome.[18] Examination of nailbed capillaries help in the diagnosis of dermatomyositis and lupus erythematosus.

Oral mucosa

The involvement of oral mucosa is absent in the majority of diseases causing erythroderma. The oral mucosa is spared in SSSS, and it differentiates CCC from neonatal candidosis. The presence of mucositis and cheilitis should suggest drug hypersensitivity reactions or nutritional deficiencies.

Cutaneous examination clues

The recognition of diagnostic clinical clues is very crucial in the diagnosis of causes of erythroderma (Figures 11

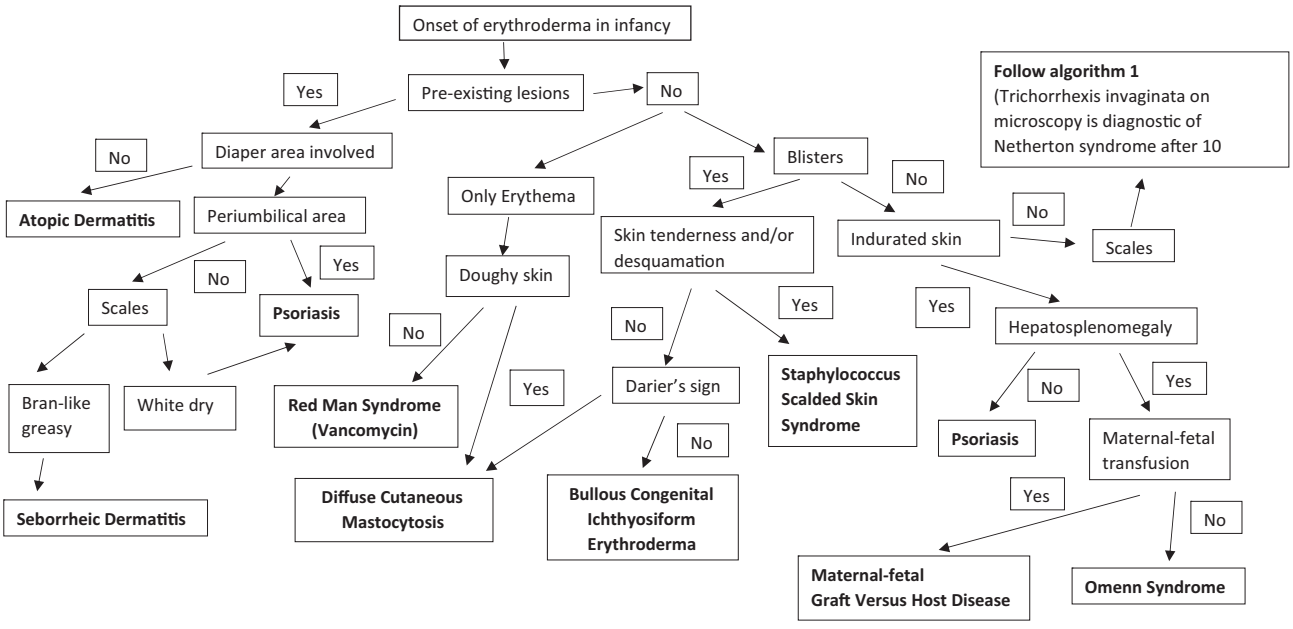

Fig 14 An algorithmic approach to differential diagnosis of erythroderma presenting during infancy.

and 12). These include characteristic clinical features, clinical signs, and clinical tests (Tables 3, 5-7).

Systemic examination

Detailed history and cutaneous examination findings help in identifying underlying cause and severity of erythroderma. The general physical and systemic examination gives additional diagnostic clues and prognostic clues (Table 8). The involvement of other organ systems is common in syndromic congenital ichthyosis, primary immunodeficiency, metabolic disorders and malignancy. Erythroderma results in hemodynamic changes and secondary bacterial infections, especially in extremes of age groups.

Laboratory investigations

Simple and relevant laboratory investigations, like a potassium hydroxide (KOH) preparation and staining, aid in confirming the clinical diagnosis. KOH preparation helps demonstrate fungal elements in CCC and dermatophytoses, and mites in crusted scabies. Gram staining of pustules confirms the diagnosis of candidosis or secondary bacterial infections. Pemphigus foliaceous can be diagnosed by the demonstration of acantholytic cells on a Tzank smear. Characteristic trichorrhexis invaginate, also known as "bamboo hair," can be seen upon microscopic examination of hairs in infants with Netherton syndrome. Dermatoscopic examination, a noninvasive method of visualizing subepidermal structures, supports the diagnosis of preexisting dermatoses. It is also very useful in identifying hair and nail changes, including nailbed capillary changes.

Conclusions

Erythroderma is a diagnostic and therapeutic challenge in the majority of cases. It is a dermatologic emergency, necessitating immediate therapeutic intervention. The diagnosis of the underlying cause of erythroderma and early recognition of consequences of erythroderma are crucial in reducing associated morbidity and mortality. The diagnostic and prognostic clues can be revealed by a detailed history and thorough clinical examination. Important features that are vital in the differential diagnosis include age at onset, as well as the cutaneous and systemic examination findings. An algorithmic approach simplifies the clinical evaluation of erythroderma, especially in neonates (Figure 13) and infants (Figure 14). Further evaluation of the patient with basic or advanced laboratory investigations is required to confirm the clinical diagnosis and to monitor the progression and consequences of erythroderma.

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