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Erythroderma (exfoliative dermatitis) part one: underlying causes, clinical presentation and pathogenesis

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Abstract

Erythroderma (exfoliative dermatitis), first described by Von Hebra in 1868, manifests as a cutaneous inflammatory state, with associated skin barrier and metabolic dysfunctions. The annual incidence of erythroderma is estimated to be 1 to 2 persons per 100,000 population in Europe with a higher male-to-female ratio. Erythroderma may present at birth, develop acutely or insidiously (due to progression of an underlying primary pathology, including malignancy). Whilst there is a broad range of diseases that associate with erythroderma, the vast majority of cases result from pre-existing and chronic dermatoses. In part one of this two part concise review, we explore the underlying causes, clinical presentation, pathogenesis and investigation of erythroderma, and suggest potential treatment targets for erythroderma with unknown causes.

Introduction

Erythroderma (exfoliative dermatitis) represents a dermatological emergency, and presents with extensive erythematous skin and scaling, affecting ≥90% of body surface area. First described by Von Hebra in 1868, erythroderma represents a cutaneous inflammatory state, with associated dysfunction of both the skin barrier and metabolic processes. Many diseases associate with erythroderma. Most cases result from pre-existing and chronic dermatoses.[1] In part one of this

concise review, we explore the underlying causes, clinical presentation, pathogenesis and investigation of erythroderma, and suggest potential treatment targets for erythroderma with unknown causes.

Underlying causes of erythroderma

Erythroderma manifests from severe skin dysmetabolism, reported in severe forms of a range of diseases that could be broadly categorised into congenital, infective, inflammatory, immunobullous, neoplastic, iatrogenic and idiopathic causes. Table 1 shows the range of diseases associated with the clinical presentation of erythroderma, including key clinical features and reading references. Commonly, erythroderma results from exacerbations of pre-existing dermatoses, such as psoriasis or eczema. Psoriatic erythroderma may result from sudden withdrawal of systemic or very potent topical corticosteroids. Drug-related erythroderma eruptions are often caused by anticonvulsants, antibiotics and topical preparations[2] A detailed chronological history, including clinical improvement upon drug cessation, are essential for the determination of the causative drug, which can often prove challenging.[2] Table 2 shows the distribution of the various causes of erythroderma. Despite our knowledge and understanding of the many and varied causes of erythroderma, the precise cause may not be established in up to one in six cases.[2]

Clinical presentation of erythroderma

Erythroderma may present at birth, and develops either acutely (e.g. due to infection or drugs), or more gradually due to the progression of an underlying primary pathology, including dermatoses and malignancies.[2] Associated signs and symptoms may give further clues to the underlying aetiology of erythroderma.

Congenital erythroderma may co-present with a diversity of cutaneous and extra-cutaneous clinical features at birth and later on in life. In the case of autosomal recessive congenital ichthyosis, affected infants may co-present with collodion membrane, ectropion, eclabium and folded ears at birth, which may be further complicated by hair and nail abnormalities, hypohidrosis and skin contractures in the case of Harlequin Ichthyosis. In Netherton syndrome, the skin have the characteristic ‘double edged’ ichthyosis linearis circumflexa appearance; the hair shaft is abnormal and brittle (trichorrhexis invaginata) and affected children have a predisposition to atopy. Developmental delays in children born with congenital erythroderma should always prompt

the screening of syndromic forms of congenital ichthyosis and neutral lipid storage disease (e.g. Chanarin-Dorfman syndrome). In erythroderma due to primary acrodermatitis enteropathica, the presentation of perioral and perianal dermatitis may not present until after affected infants begin to wean off breast milk. Congenital erythroderma may also co-present in severe combined immunodeficiency, a rare disease associated with alopecia, chronic diarrhoea, failure to thrive, lymphadenopathy and hepatosplenomegaly.

Acute erythroderma usually manifests clinically as widespread erythema, followed by exfoliative scaling over the subsequent 2-6 days.[3] The morphology of the rash preceding erythroderma varies significantly according to the underlying cause and particular attention to co-presenting symptoms is required to aid in diagnosis of the underlying cause. Viral exanthems typically presents as an acute morbilliform macular and/or maculopapular eruption spreading in a cephalocaudal direction. Drug eruptions may begin as a morbilliform or urticarial rash, which can further develop pustules at flexural sites (in acute generalised exanthematous pustulosis), lymphadenopathy (in drug reaction with eosinophilia and systemic symptoms) or mucocutaneous skin erosions and blistering (in Stevens-Johnson syndrome and toxic epidermal necrolysis). Patients presenting with erythrodermic psoriasis may co-present with severe nail dystrophy. Erythroderma due to underlying immunobullous disease may present with intact and de-roofed mucocutaneous blisters or erosions. Erythroderma in the context of unexplained weight loss, lymphadenopathy and presence of atypical lymphocytes (in blood film) in absence of pre-existing skin diseases should prompt consideration of underlying malignancies such as Sézary syndrome.

Thermoregulatory disturbances (fever and chills), reactive lymphadenopathy and superimposed bacterial infections may occur concurrently with erythroderma from all causes. In extreme cases, sequelae of erythroderma include hypovolaemia (with reflex tachycardia), high-output cardiac failure, anaemia, electrolyte disturbances, and acute respiratory distress syndrome.[3,4]

Pathogenesis of erythroderma

Congenital erythroderma: Disorders of lipid metabolism underpin the pathogenesis of a range of differential causes of congenital erythroderma. Reviews by Elias et al (2008) and Radner et al (2013) extensively discuss the pathogenesis of genodermatoses secondary to abnormalities and

dysregulation in fatty acid metabolism, cholesterol metabolism, triglyceride metabolism and lipid transportation.[5,6] In brief, disordered lipid metabolism leads to abnormal lipid organisation within the stratum corneum, therefore, interfering with normal lateral packing of lipids, which is crucial for the barrier function of the skin.[7] This abnormality has been observed in lamellar ichthyosis and atopic dermatitis.[8]

Acquired erythroderma: The pathogenesis of acquired erythroderma is poorly understood. Studies suggested that factors such as an increase in serum immunoglobulin E, interleukin-4 and interleukin-10 associated with Th1/Th2 imbalance in favour of Th2 differentiation and dysregulated angiogenic factors could have a role in the pathogenesis of erythrodermic psoriasis.[9] Interleukin-4 and interleukin-13 signalling are central to the pathogenesis of atopic dermatitis and other atopic diseases through activation of downstream IgE dependent processes that leads to activation of mast cells and eosinophils and the clinical presentation of skin inflammation.[10] Indeed, dermal eosinophilic infiltrates is a characteristic histological feature observed in skin biopsies from patients with erythrodermic atopic dermatitis[11] and this finding may also be observed in allergic contact dermatitis, urticaria, immunobullous diseases and dermal hypersensitivity reaction patterns.[12] Interleukin-4 and interleukin-13 are targets for blockade by dupilumab, a licensed biologic treatment for moderate to severe atopic dermatitis.

The pathogenesis of erythroderma in patients with haematological malignancies is poorly understood and the changes to cytokine signalling profile in this group of patients is highly complex. Nevertheless, there is an increase in the Th2 profile of cytokines such as interleukin-4, interleukin-5 and interleukin-10 in the skin and serum of patients with Sézary syndrome;[13] overexpression of interleukin-13 signalling in cutaneous T-cell lymphoma;[14] and upregulation of interleukin-4 signalling in the bone marrow in patients with acute myeloid leukemia.[15] The link between interleukin-4 and interleukin-13 signalling in the pathogenesis of erythroderma in patients with haematological malignancies remains speculative given the lack of relevant studies.

Regardless of the underlying cause of erythroderma, there is an increase in expression of adhesion molecules (increased VCAM-1, ICAM-1, E-selectin and P-selectin expression found on endothelium in-situ in patients with erythroderma, mycosis fungoides and atopic dermatitis)[16] and

pro-inflammatory mediators stimulating dermal inflammation and epidermal turnover rate, which shortens the keratinocyte transit time through the epidermis, resulting in exfoliation.[1]

Discussion

Our literature review identifies that globally, the most common cause of erythroderma is due to an underlying primary skin disease. However, to the best of our knowledge there is no recent UK data about the differential causes of erythroderma[2]. Therefore, advancement of our current clinical management of erythroderma is reliant upon developing our knowledge of the underlying pathogenesis in order to identify possible targets for therapeutic intervention. Identification of specific raised molecular cytokines may allow us to subtype erythroderma cases and manage accordingly. The pathogenesis of erythroderma remains unclear but the interleukin-4 and interleukin-13 pathways appear to be an attractive potential treatment target for managing erythroderma with unclear cause.

Conclusion

A wide range of diseases can lead to erythroderma but its pathogenesis remains poorly understood.

Learning Points

- Infants presenting with erythroderma at birth or within the first year of life should always prompt the consideration of inherited metabolic diseases.
- Pre-existing dermatoses (particularly psoriasis and eczema) underlie a significant proportion of cases of erythroderma, as shown in the current literature to date.
- Regarding the acute presentation of erythroderma, the morphological nature of the rash preceding erythroderma and co-presenting symptoms are of great significance to aid in aetiological diagnosis.
- In erythrodermic psoriasis, studies have suggested factors such as increased serum immunoglobulin E, interleukin-4 and interleukin-10 associated with favoured Th2 differentiation and dysregulated angiogenic factors could have a role in the pathogenesis.

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Table 1. Diseases associated with erythroderma and useful diagnostic features.

Table 2. Literature review of the differential causes of erythroderma from different geographical locations worldwide.

Category	*Examples*	*Useful diagnostic features and investigations*	*Useful references to read*
Congenital	Ichthyosis and keratinopathies • Syndromic forms without skin blisters such as: – Netherton syndrome (AR), – Sjögren-Larsson syndrome (AR) – Dorfman-Chanarin syndrome (AR) – Refsum syndrome (AR), – Keratitis-ichthyosis-deafness (KID) syndrome (AR) – Conradi-Hünermann-Happle syndrome (XLD) – Congenital hemidysplasia with ichthyosiform erythroderma and limb defects (CHILD) syndrome (XLD) – Ichthyosis follicularis, atrichia and photophobia (IFAP) syndrome	Clinical History: Starts at birth. Inherited forms of acrodermatitis enteropathica may commence after the infant weans. Clinical signs: Collodion membrane may be present at birth in syndromic and non-syndromic forms of congenital ichthyosis. Recessive X-linked ichthyosis only affects males and typically presents with generalised scale within 6 months of birth, and may co-present with undescended testicles and corneal opacities. Investigations: Relevant gene panels. Serum immunoglobulin level in Omenn syndrome. Serum zinc level in inherited forms of acrodermatitis	Hoeger and Harper, 1998[17] Dhar et al, 2012[18] Nacim et al, 2019[19]

	(XLR and AD) – X-linked ichthyosis (XLR) • Non-syndromic forms such as: – Lamellar ichthyosis (AR) – Non-bullous congenital ichthyosiform erythroderma (AR) – Harlequin ichthyosis (AR) • Non-syndromic forms with blistering such as: – Epidermolytic ichthyosis (AD and AR) Immunodeficiency syndromes • Omenn syndrome (AR) • Hyper IgE syndrome Metabolic disorders • Holocarboxylase synthetase deficiency (AR) • Inherited form of acrodermatitis enteropathica (AR)	enteropathica.	

Inflammatory	Eczema Psoriasis Pityriasis rubra pilaris (PRP) Seborrhoeic dermatitis	Clinical History: Associated atopy. Family history of atopy or psoriasis. Previous clinical diagnosis of dermatosis. History of dystrophic nails and inflammatory arthropathy may favour a diagnosis of psoriasis. PRP typically presents with palmoplantar keratoderma. Clinical signs: Palmoplantar keratoderma in PRP. Nail pitting and dystrophy in psoriasis. Investigations: Full blood count (especially eosinophil count) and skin biopsy. HIV screening in severe seborrheic dermatitis. Atopic dermatitis: total immunoglobulin E level	Akhyani et al, 2005[20] Mathew et al, 2017[21]
Immuno-bullous	Subcorneal • Pemphigus foliaceous (PF) Intraepidermal • Pemphigus vulgaris (PV)	Clinical History: BP may presents with a pre-bullous stage with widespread urticated pruritic plaques before blistering commence. History of	Scrivener et al, 1998 [22]

	Sub-epidermal • Bullous pemphigoid (BP)	oral and genital ulceration is a key history in PV. Patients may not report any blisters in PV and PF. Clinical signs: Scale, crust, erosion, typically confined to the skin in PF but sparing the mucosa. Urticated plaques, larger intact and deroofed bullae in BP. In PV, mucosal erosions and ulceration is a key feature and may or may not affect the skin. Investigations: Skin histology: BP shows subepidermal blistering; PF and PV shows intraepidermal blistering. Skin direct immunofluorescence microscopy (IMF): PV and PF shows intercellular surface staining pattern; BP shows linear basement membrane zone pattern. ELISA: key features are desmoglein 1 in PF; desmoglein 3 in PV; BP180 and BP230 in BP.	

Infective	Human immunodeficiency virus (HIV) Scabies Staphylococcus scalded skin syndrome (SSSS)	Clinical History and signs: HIV- opportunistic and recurrent infections Scabies- widespread pruritis and erythematous rash with burrows on dermoscopy. SSSS- fever, malaise and widespread fluid-filled blistering rash. Investigations: HIV- CD4 count and HIV viral load. Scabies – dermoscopy to identify burrows; skin biopsy to identify mites. SSSS - skin biopsy (intraepidermal cleavage at granular layer), microbiology skin swabs and blood culture	Mathew et al, 2017[21] Bowles et al, 2019[23] Paparizos et al, 2019[24]
Neoplastic	Cutaneous T-cell lymphoma B cell lymphoma Paraneoplastic pemphigus Malignancies, especially, haematological and solid organ	Clinical History and signs: Unexplained weight loss, lymphadenopathy, pruritus Investigations: Blood test screening Flow cytometry Skin biopsy Lymph node/ Bone marrow biopsy	Lim et al, 2018[25]

Immune	Hypersensitivity • Contact dermatitis • Erythroderma multiforme major (EM-major) • Steven-Johnson syndrome (90% cases) Immunodeficiency • Graft-versus-host disease (GvHD) Autoimmune • Systemic lupus erythematosus (SLE)	Clinical History and signs: EM-major: about 90% cases caused by infections (especially Herpres virus) and 10% caused by drugs; presenting as target like erythematous lesions and polymorphous rash. SJS: 90% cases associated with infections and typically presents with mucocutaneous skin erosions and conjunctivitis. History of allogenic transplant in GvHD. Acute GvHD occurs within 3 months of transplantation and may be associated with gastrointestinal and liver dysfunction. Chronic GvHD may associate with dry eyes, scleroderma, hair loss, nail dystrophy, liver, lung and gastrointestinal dysfunction. Extra-cutaneous features in SLE can include arthritis, pleurisy, pericarditis, kidney disease, neuropathy, etc. Investigations: Blood test screening –	

		autoantibodies. Skin biopsy. Patch testing in contact dermatitis.	

Iatrogenic	Drugs such as antibiotics, anticonvulsants, antimalarials, allopurinol, lithium, barbiturates Erythroderma multiforme major (10% cases) Drug reaction with eosinophilia and systemic symptoms (DRESS) Steven-Johnson Syndrome (10% cases) Toxic epidermal necrolysis Acute generalised exanthematous pustulosis (AGEP)	Clinical History: May present with systemic symptoms such as malaise, fever Clinical signs: Lymphadenopathy and hepatosplenomegaly may present in DRESS syndrome. Pustular lesions developing at flexural sites may suggest AGEP or bacterial skin infection. Investigations: Blood test screening for eosinophilia and deranged liver function test. Skin biopsy.	
Nutritional	Acrodermatitis enteropathica (inherited or acquired)	Clinical History: Poor nutrition, excess alcohol, history of malabsorption Clinical signs and symptoms: Triad of psoriasiform dermatitis of circumoral or periorificial areas, alopecia and diarrhoea. Investigations: Blood test screening for nutritional deficiencies.	Hoeger and Harper, 1998[17]

Others	Cutaneous mastocytosis Hypereosinophilic syndrome Sunburn	Clinical history and sign: Mastocytosis: rubbing an area of affected skin can activate mast cells leading to skin inflammation (Darier sign). Investigations: Skin biopsy and haematological assessment in mastocytosis and hypereosinophilic syndrome.	

AR = autosomal recessive; AD = autosomal dominant; XLD = X-linked dominant; XLR = X-linked recessive

Table 1. Diseases associated with erythroderma and useful diagnostic features.

Description of study	*Differential causes*	*Demographics (Age and sex)*	*Reference*
Case series 97 patients with acquired erythroderma in Iran	59.7% Dermatoses 21.6% Drug reactions 11.3% Malignancies 7.2% Idiopathic	Median age at diagnosis 46.2 years Male: Female ratio 1.85:1	Akhyani et al, 2005[20]
Case series 49 patients with acquired erythroderma in Thailand	38.77% Drugs 27.5% Dermatoses	Median age at presentation 51.7 years Male: Female ratio 2:1	Leenutaphong et al, 1999[26]
Case series of 309 patients in Brazil	20.7% Eczema 16.8% psoriasis 12.3% Sezary syndrome 12.3% Drug eruption 8.7% Atopic dermatitis 5.5% Mycosis fungoides 6.8% Others 16.8% Idiopathic	Median age 57 years Male: Female ratio 2.2	Miyashiro and Sanches, 2020[2]

Case series of 25 patients in Porur, India	32% Psoriasis 24% Drugs 12% Eczema 8% Hereditary disorders 4% Pemphigus foliaceus 12% Others (including malignancy, Dermatophytosis, SSSS and Pityriasis rubra pilaris)	Age range of 5 days to 72 years. Peak incidence 21-30 years (24%) Male: female ratio 1.5:1	Sudho et al, 2003[27]
Case series of 370 patients in Kerala, India	32.7% Psoriasis 15.9% Contact dermatitis 15.7% Idiopathic 8.1% Chronic actinic dermatitis 6.5% Drugs 6.5% Atopic dermatitis 3.2% Malignancy 3.2% Pityriasis rubra pilaris 1.4% Pemphigus foliaceus 0.8% Other- including crusted scabies and congenital ichthyosiform erythroderma	Male: Female ratio of 3.6: 1 Mean age of onset of erythroderma was 55.38 ± 16.67 (range 3-91 years) years	Mathew et al, 2017[21]
Case series of			Yuan et

82 patients in China	72% Pre-existing dermatoses (30.5% Psoriasis) 17% Drug Reactions 6.1% Idiopathic causes 4.9% malignancies		al, 2010[28]
Retrospective study of 80 erythrodermic adults in Africa	51.25% Psoriasis 11.25% Drugs 8.75% Malignancy 7.5% Idiopathic 6.25% Pemphigus foliaceus 2.5% Contact Dermatitis 1.25% Pityriasis rubra pilaris 1.25% Pemphigus foliaceus	Male: Female 2.2: 1.0 Average age 53.78 +/- 18 years.	Rym et al, 2005[29]
Case series of 90 patients in Pakistan	37.8% Psoriasis 14.6% Idiopathic 7.8% Congenital ichthyosiform erythroderma 5.6% Pemphigus foliaceus 5.5% Drugs 5.5% Malignancy 3.3% Atopic dermatitis 3.3% Contact Dermatitis 2.2% Crusted Scabies 2.2% Pityriasis rubra pilaris	Male: Female ratio of 2.8: 1 Mean age of onset 41.6 years	Pal et al 2002[30]

Table 2. Literature review of the differential causes of erythroderma from different geographical locations worldwide.