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ACQUIRED ERYTHRODERMA

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Erythroderma /exfoliative dermatitis/ is an inflammatory process affecting 90% of the total body surface area. Erythema, infiltration and desquamation are the main clinical features of the syndrome. It appears in the context of many dermatological and systemic disorders, as well as neoplastic proliferation of either skin or internal parenchymal organs. Erythroderma is a life-threathening condition which requires emergent complex measures. Herein a short overview of the clinical, pathogenetic, diagnostic and therapeutic characteristics of the syndrome is presented.

Key words: erythederma, exfoliative dermatitis

Erythroderma is an inflammatory process that affects more than 90% of the total body surface. The most characteristic clinical featureste of the syndrome are erythema, infiltration and desquamation. The term exfoliative dermatitis is used interchangeably with the classic Latin description, while cases of erythroderma in association with palmo-plantar keratoderma, dermopathic lymphadenopathy, and elevated levels of immunoglobulin E (IgE) are depicted as "red man syndrome" (Brady et al. 2000). The term l'homme rouge refers to exfoliative dermatitides that occur in the context of primary T-cell lymphomas, and most often manifest with erythro-livid infiltarion of intensive itch and bad prognosis (Freedberg, 1987).

Classification

Bazin (1866) made the first scientific attempt to classify erythrodermas as primary (idiopathic) and secondary (that occur in the course of pre-existing dermatosis). Wolters (1912) defined the acquired forms as symptomatic. In 1928 Darier specified three groups of exfoliative dermatitides according to their clinical course: acute, subacute (Wilson-Brocq), and chronic (Wilson-Brocq, pityriasis rubra Hebra-Jadassohn, pre-mycotic and leukemic). Degos (1953) described two clinical forms of erythroderma: erythemo-squamous and vesiculo-bullous, and classified them as primary (dermatitis exfoliativa Wilson-Brocq и pityriasis rubra Hebra), secondary (psoriasis vulgaris, lichen ruber planus, eczema, pityriasis rubra pilaris, pemphigus foliaceus), drug-induced (As, Bi, Hg), infectious, pre-mycotic, and leukemic. The first clinico-pathologic correlation appraoch in the erythroderma classification was made by Herzberg in 1958. According to him, five forms: pityriasis rubra Hebra-Jadassohn typev (pityriasiform desquamation, nail changes, and alopecia), melanoerythroderma of the elderly, dermatitis exfoliativa Wilson-Brocq type (lamellar ex foliation, lymphadenopathy, alopecia, and nail changes occurring as a complication of contact dermatitis, or pyogenic infection), erythema scarlatiniforme recidivans (drug-induced erythroderma), and vesiculo-bullous erythroderma with toxic shock syndrome and bad prgnosis should be distinguished.

The first Bulgarian observations on erythroderma appeared in 1967 (Pophristov and Zlatkov), who published a broad overview of 67 clinical cases and summarized their 25-year experience into a pathogenetic attempt for classification. According to these authors the following types of erythroderma exist: 1. exfoliative dermatitis occurring in the course of pre-existing dermatoses (psoriasis vulgaris, eczema, pityriasis rubra pilaris, lichen ruber planus, etc.); 2. erythroderma as a complication of lymphoproliferative disorder (primary T cell cutaneous lymphoma, mycosis fungoides, morbus Hodgkin, leukemias); 3. toxo-allergic erythrodermas (drug-induced); infectious types (bacterial,

Table1. Acquired erythroderma etiology

Dermatoses
dermatitis/eczema (atopic, contact, seborrheic, stasis, etc), psoriasis, pityriasis rubra pilaris, pemphigus foliaceus, morbus Hailey-Hailey, pemphigoid, lichen planus, lupus erythematosus, mycosis fungoides, dermatophytosis, scabies, sarcoid, toxic shock syndrome
Systemic diseases
Lymphoma, leukemia, multiple myeloma, internal organs carcinomas
Drugs
dimercaprol, codeine, captopril, diphenylhydantoin, carbamazepine, hexaquine, aztreonam и clindamycin, bevacizumab, enalapril, quinidine, minocycline, isoniazid, beta lactames, gold salts, barbiturates, anti psychotic drugs, Ca antagonists, etc.
Infectious
Bacterial SSSS, erythema scarlatiniformis recidivans
Fungal: Candidiasis
Protozoic: Scabies

mycotic, viral, protozoal); 4. erythrodermas occurring as a complication of a systemic disorder (hepatic, renal, endocrine, etc.); 5. miscellaneous (idiopathic).

Etiology

Malignant lympho-proliferative disorders, (Kim et al, 2006), gastro-intestinal dysfunction (Kameyama et al., 2005), nephrotic syndrome (Kagan et al., 1999), diabetes mellitus (Bouwhuis et al., 2002), adrenal, sexual,pituaryvdisorders (Herzberg, 1958), macroglobilinemias (Sutton, 1956), infections and intoxications (Duperrat, 1959), iatrogenic reasons (Degos, 1960) and alcohol abuse (Bader, 1999) are all suggested as potential cause for exfoliative dermatitis.

Epidemiology

Hasan and Jansen (1983) reported an exfoliative dermatitis US incidence of 1-2 /100 000, which increased to 35/100 000 in the dermatologically affected population. The Dutch incidence is found lower 0.9/100 000 (Sigurdsson, 2001), however, the lowest incidence is reported out of Tunisia – 0.3/100 000 (Rym, 2005). Men are more often affected: 1.85 (in Iran), 2.2 (in Tunisia), 2.3 (in Bulgaria), 2.6 (in Switzerland – Eugster, 2001) to 4 (in Spane, Botella-Estrada, 1994). No racial predisposition is reported. The disease onset is in the four decade of life, with a medium onset age of 41.9 years (Sehgal, 1986) to 61 years (Hasan, 1983). Botella-Estrada et al. (1994), Hasan et al. (1983) and Sehgal et al. (1986) observed slow, and gradual onset of the syndrome, with the exception of drug-induced, lymphoma, and staphylococcal scalled skin syndrome cases which disseminated rapidly over no more than 48 hours. 33.3% of all erythrodermas begin spontaneously, while the rest 66.7% result from the distribution of a previously existing dermatosis.

The higher incidence of symptomatic erythodermas that occur in the context of malignancies or severe systemic disorders requires thorough work-up of all patients, regretting the history of a pre-existing dermatosis (Eugster et al., 2001). Morar et al. (1999) detected higher incidence of exfoliative dermatitis in HIV-positive patients, suggesting this as a result of either polypragmasia or dermatological complications. The authors concluded that every erythroderma in a black man should be screened for HIV infection. Erythroderma is a life-threatening condition that should be treated in a intensive care unit with all the prerequisites of a potentially lethal disorder. 43% of all generalized exfoliative dermatitis cases die. An accent should be given to a state of fever which is found to be the most sensitive negative prediction factor (Byer et Bachur, 2000).

Pathophysiology

Sigurdsson et al. (2000) detected dysbalanced dermal cytokine profile in both inflammatory and neoplastic erythodermas. Interferon gamma (IFN-gamma) is persistently increased in all cases of idiopathic and atopic dermatitis relevant exfoliative dermatitides. The lymphoma cases always demonstrate elevated levels of interleukin 4 (IL-4)-antigen presenting cells. The dermal inflammation in the primary T-cell lymphomas is considered to be ofvTh2 profile, in contrast with the prevalence of Th1 cytokines in the benign forms of erythroderma. Fierro et al. (2006) gave further insight of the pathogenesis of inflammatory exfoliative dermatitis demonstrating significant increase in CCR5 and CXCR3 in the lymphocytes of dermal tissue sections. Obviously, the two main types of erythroderma – inflammatory and neoplastic – have been caused by diametrically opposite immuno-pathological trends. The Th1 prevalence in benign erythroderma cases may be a result of potentiated viral infection. Moreover, Huang et al. (2006) proved significant reactivation of human herpes virus 6 (HHV 6) in 35% of idiopathic erythroderma cases to none in healthy controls ($p<0.001$).

Table 2. Acquired exfoliative dermatitis etiologic distribution

References	Pre-existing dermatoses	drug-induced	malignancies	idiopathic
Pophristov et al, 1967	50	8.3	26.7	10
Nicolis et Helwig, 1973	25	42	21	12
Hasan et Jansan, 1983	42	22	4	32
Sehgal et Srivastava, 1986	52.2	24.7	0	22.5
King et al, 1986	30	34	20	16
Sigurdsson et al, 1996	53	5	13	26
Pal et Haroon,1998	74.4	5.5	5.5	14.6
Eugster et al., 2001	58	16	11	15

Histological findings

The duration and severity of the inflammatory changes rather than the pre-existing dermatology specific features are the most important factors to influence the histomorphological substrate (Cohen et al., 1997). The acute stage characterizes with spongiosis, parakeratosis,

and mixed infammatory infitrate in the edematous papillary dermis. The chronic histology changes encompass psoriasiform dermatitis features with prominent acanthosis and elongation of rete ridges. The neoplastic erythroderma could show some pleomorphic infiltrate with or without obscuration of the dermo-epidermal junction and lichenoid inflammation of atypical cerebriform lymphoid cells with epidermotropism and Putrier microabscess formation (Shaikh et Rahman, 2006). Although unspecific, papillomatosis and confluent rete ridges could be signs of pre-existing psoriasis. Superficial acantholysis occurs in cases of pemphigus foliaceus and staphyloccocal scalded skin syndrome (Scrivener et al., 1998). Vertically and horizontally alternating parakeratosis verifies pityriasis rubra pilaris. Plentifulness of eosinophils interstially and around papillary vessels suggest drug-induced process or hyperoesinophilic syndrome (Brady et al, 2000).

characteriztic for eczematic states, lichen planus, and drug-induced cases, and does not appear in psoriasis and pityriasis rubra pilaris. Nail dystrophy and subungual hyperkeratosis most often develop in pityriasis rubra pilaris and mycosis fungoides, in the clinical picture of the latter cicatricial alopecia and mucinosis follicularis are commonly seen. Pal and Haroon (1998) found out that mucosal changes occurred most frequently in cases of lichen planus and drug-induced erythrodermas. Periorbital erythema and fine desquamation is seen in contact and atopic dermatitides, and ectropion and epiphora are common complications. According to Rook et al. (1987) liver and spleen enlargement occur in mycosis fungoides, drug reactions and pityriasis rubra pilaris. Intact skin islands could be seen both in pityriasis rubra pilari and psoriatic erythroderma. Ofuji papuloerythroderma features the deck-chair sign and often has wheals flares (Pullmann et al.,

Table 3. Specific clinical symptoms of pre-existing dermatosis erythroderma

Symptom	Psoriasis	Lichen planus	Pityriasis rubra pilaris	Drug reaction	Eczema	Papuloerythro-dermia Ofuji	Mycosis fungoides
Itch		+		+	+	+	+
Lymphadenopathy						+	+
Intact skin islands	+		+				
Periorbital changes					+		
Mucosal involvement		+		+			
Nail lesions			+				+
Cicatricial alopecia		+					+
Deck chair sign						+	
Visceral involvement			+	+			+

Clinical findings

Unspecific clinical findings and low clinico-pathological correlation are the most important features of erythroderma. Botella-Estrada et al. (1994) proved that only in 10% of all pre-existing dermatosis erythroderma cases without previous history, the specific clinical entity could be verified. Moreover, the process of verification requires series of histology and clinical observations. Along with erythema and exfoliation, which are obligatory, Akhyani et al. (2005) found that 97.5% of all cases with erythroderma had pruritus, lymphadenopathy (21.3%), edema (14.4%), hyperkeratosis (7.2%) and mucosal involvement (1%). Pityriasiform desquamation is seen in seborrheic and contact dermatitis. Lamellar desquamation occurs in cases of pemphigus foliaceus and malignant lympho-proliferative skin disorders. The most intensive and therapy-resistant itch associates mycosis fungoides, lichen ruber planus, and drug-induced dermatoses, while the psoriatic erythroderma is asymptomatic. Dermatopathic lymphadenopathy is

2004). Mammary gland proliferation, probably due to secondary hyperestrogenemia, could be a complication of long-lasting, refractory erythroderma (Shuster et Brown, 1962). Vomitus, fatigue, faintness, and fever are the most common constitutional symptoms of erythroderma. The old age and metabolic disturbances that complicate the course of the disease, lead to cardiac arrest, peripheral circulatory insufficiency and thrombotic incidences. The patients become immunocompromised in the course of the diseases and commonly develop skin, soft tissue and pulmonal infections. Pneumonias are the most frequent cause for death in erythroderma patients.

Diagnosis

Verification is clinical.According to Walsh et al. (1994) the microscopic identification of spongiotic dermatitis, mycosis fungoides and psoriasis as causes of erythroderma is easier than that of drug-induced exfoliative dermatitis and pityriasis rubra pilaris. Remarkably, the epidermotropism which is con-

sidered the most important sign of neoplastic lymphoid proliferation has been proven to occur in other cases of lichenoid dermatitis, such as drug-induced or viral, therefore it should be referred to as a misleading pathomorphological feature. Serial biopsies and step sections are required to improve the specificity of the histological examination. Recently, an attempt for introducing new cytology approaches in the distinction of inflammatory and neoplastic orgini of erythroderma is made.
Immunohistochemistry is required is cases of pleomorphic lymphoid proliferations and lymphoma suspicion. However, in his large study of erythrodermic T-cell lymphomas and their benign inflammatory simulators, Vonderheid (2006) defined the immunohistochemistry approaches as unreliable and non-specific.
First Cordel et al. in 2001 introduced molecular-genetic methods in verification of erythroderma diagnosis. Detection of monoclonal lymphoid proliferation in the blood and tissue sections is of utmost significance in the work-up of erythrodermic lymphoma patients. Vonderheid (2005) suggested that CD4+CD7- and CD4+CD26- phenotype of peripheral T-lymphocytes is characteristic for primary cutaneous T-cell lymphomas. Flow-cytometric detection of abnormal lymphoid populations in the peripheral blood of patients with Sezary syndrome serves as highly sensitive and specific criterion for treatment efficacy and prognosis. (Morice et al., 2006). In conclusion, the clinical, histological, and flow-cytometric findings are the most important tools for differentiation of malignant and benign exfoliative dermatitides. Immunohistochemistry and molecular approaches could only further confirm and specify the diagnosis.

Therapy

Erythroderma is a life-threatening condition that should be treated in an intensive care unit. Rehydratation and protein expansion is needed in accordance with 24-hour diuresis and edematous conditions. Minimal number of medications should be introduced, since many of them could deteriorate or cause drug-induced erythroderma. Topical therapy of emollients, antiseptic baths, and cool dressings is preferable (Rothe et al., 2005). Protein-rich diet with fol ate supplementation should be introduced. The anti-inflammatory and catabolic nature of corticosteroids make them a first-line therapy (Horiuchi, 2000). Etilogical treatment should be considered in cases with a well-known history of a pre-existing dermatosis. Biological therapy has been proven beneficial in psoriatic erythroderma (Lewis et al., 2006). Daclizumab has been successfully used in lympho-proliferative cutaneous disorders (Osborne et al., 2006).

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