

Diagnostic Role of Direct Immunofluorescence Assay in Determining The Etiology of Erythroderma: Experience in a Tertiary Referral Hospital

Ecem Bostan MD¹, Ozay Gokoz², Sibel Dogan¹, Duygu Gulseren¹, Neslihan Akdogan¹, Basak Yalici-Armagan¹, Sibel Ersoy-Evans¹, Gonca Elcin¹, Aysen Karaduman¹

¹ Department of Dermatology and Venereology, Hacettepe University, Faculty of Medicine, Ankara, Turkey

² Department of Pathology, Hacettepe University, Faculty of Medicine, Ankara, Turkey

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Corresponding author: Ecem Bostan, MD, Hacettepe University, Faculty of Medicine Department of Dermatology and Venereology, Ankara, Turkey, Phone:03123051704, Fax: 0 3123054127, E-mail: bostanecem@gmail.com

ABSTRACT **Introduction:** Erythroderma is a life-threatening dermatologic emergency which is characterized by diffuse erythema and exfoliation affecting more than 90% of the body surface area. Most common cutaneous diseases associated with erythroderma are systemic contact dermatitis, psoriasis, drug eruption and atopic dermatitis. Clinical-pathological correlation is used to determine the underlying disease. In addition, direct immunofluorescence (DIF) may provide significant clues for etiology of erythroderma especially in the case of autoimmune bullous skin diseases (ABSDs).

Objectives: In our study, we aimed to analyze the demographic data, clinical pre-diagnoses, final diagnosis, histopathological and DIF examination findings, accompanying systemic signs and laboratory abnormalities of erythrodermic patients.

Methods: We conducted a retrospective study of 31 erythroderma patients in a referral hospital between 2014 and 2021. Cutaneous biopsies were taken from all patients for H&E and DIF examination.

Results: Average age was 54.6 ± 23 years, 48.4% of the patients were female (N = 15) whereas 51.6 % of the patients were male (N = 16). Average time between the onset of rash and biopsy was 18.8 days. DIF analysis showed immune deposits in 19.4% (N = 6) of the patients; whereas no immune deposits were detected in 80.6% (N = 25) of the patients. The most frequent final diagnosis was adverse cutaneous drug eruption followed by ABSDs.

Conclusions: Our findings suggest that DIF may be used in conjunction with clinical-pathologic and clinical findings to reveal the associated skin diseases in erythrodermic patients. Erythrodermic patients presenting with clinical findings of ABSD should be considered for DIF examination.

Introduction

Erythroderma (exfoliative dermatitis) is defined as widespread erythema and exfoliation involving more than 90% of body surface area [1]. Men seem to be more affected compared to women male-to-female ratio ranging from 1.5 to 2.8 [1-3]. Average age at the onset differs among various studies and reported to be 50.7 and 57 years in two recent reports respectively.^{3,4} Even though skin involvement is the predominant clinical picture of the condition, life-threatening systemic complications such as tachycardia, electrolyte imbalance, edema and unstable body temperature may accompany [3].

Erythroderma generally arises from the exacerbation and generalization of a pre-existing skin diseases, even though new-onset cutaneous eruptions such as adverse cutaneous drug eruptions (ACDE), psoriasis, systemic allergic contact dermatitis (SACD), autoimmune bullous skin diseases (ABSD) such as bullous pemphigoid, pemphigus foliaceus may also be the cause [3,4]. Identification of the associated cutaneous disease is not always that easy and requires longitudinal evaluation of the patient to reveal the underlying cause and manage the complications.

Histopathological examination of the lesional skin provides significant clues related to the etiology and thus may be the most fundamental evaluation to enlighten the pathogenesis of erythroderma [5]. Direct immunofluorescence (DIF), on the other hand, might prove to be quite useful in cases of ABSD and leukocytoclastic vasculitis as the suspected causes of exfoliative dermatitis by revealing the specific immune deposition pattern in the biopsies taken from the perilesional and lesional skin respectively [5,6].

In our study, we aimed to determine the diagnostic role of DIF in identifying the etiology of erythroderma and show the relationship between the presence of immune deposits and underlying diseases of exfoliative dermatitis.

Methods

The present study was a retrospective study conducted by review of electronic medical data records and histopathologic slide images belonging to 31 patients in a tertiary referral hospital between January 2014 and September 2020. Ethics committee approval was obtained (project number: GO 20/1099, decision number: 2020/19-45, decision date: November 17, 2020) and informed consent was taken from the participants for the study. All the patients were diagnosed as erythroderma and cutaneous biopsies were taken for histopathological examination and DIF analysis. Patients without histopathological and DIF examination were excluded from the study. For DIF assay, skin tissue samples were frozen in a cryostat and then sectioned with a thickness of 5 µm. Then, fluorescein-labeled

antisera against human IgM (Dako, dilution ratio: 1/20-1/40), IgG (Bio SB, dilution ratio: 1/25-1/100), IgA (Dako, dilution ratio: 1/20-1/40) and C3 (Diagnostic BioSystems Inc., dilution ratio: 1/75-1/100) were applied to sections and incubated. Presence of any positive immunofluorescence staining with IgM, IgG, IgA and C3 antisera was evaluated under immunofluorescence microscopy. Sex, age, dermatologic examination findings, accompanying systemic symptoms, clinical pre-diagnoses, laboratory findings, elapsed time between the onset of the rash and biopsy procedure, histopathologic findings, presence of immune deposits in DIF analysis, final diagnosis, treatment given and were evaluated and recorded. The underlying etiologies of erythroderma were divided into 4 categories as follows: 'category 1 (ABSD)', 'category 2 (ACDE)', 'category 3 (vascular skin diseases)' and 'category 4 (miscellaneous other skin diseases)' (Table 1). For cases with a final diagnosis of ACDE including drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, maculopapular drug eruption (MDE), Stevens-Johnson syndrome/toxic epidermal necrolysis spectrum (SJS-TEN) and vasculitic drug eruption, the most probable inciting drug/drugs were determined and time between the onset of the erythroderma and first drug intake was also evaluated.

Statistics

Statistical analyses were performed with the IBM SPSS for Windows Version 22.0 and MS Excel. Categorical variables were given as frequencies and percentages. Numerical variables were summarized as mean ± standard deviation or median (minimum-maximum).

Results

Demographical, clinical, pathological characteristics; pre-diagnoses and final diagnoses of the all study subjects along with DIF findings and laboratory abnormalities are shown in Supplementary File 1.

The average age of the subjects was 54. 6 ± 23 years (range: 3- 86 years, median: 61 years). 48.4% of the patients were female (N = 15) whereas, 51.6 % of the patients were male (N = 16). All patients presented with erythema and scaling covering > 90% of body surface area, 48.4 % of the patients (N = 15) had also one or more mucosal area (oral, anogenital and ocular) involvement. All patients with SJS (N = 4), five patients with MDE, two patients with DRESS, one patient with bullous mycosis fungoides, one patient with pemphigus foliaceus and two patients with SACD had mucosal involvement. The most common clinical presentations of oral mucosal involvement were hemorrhagic-crusted plaques covering the lips, erosions on the buccal and palatal mucosa which were predominantly observed in cases with SJS. Mucopurulent conjunctivitis, eyelid margin ulceration

and vulvovaginal/penile erosions were also present in patients with SJS. Patients with MDE, DRESS and SACD most commonly had superficial erosions on the lips as the mucosal manifestation. The most frequent systemic symptoms and signs associated with erythroderma were fever (67.7%, N = 21), followed by pruritus (38.7 %, N = 12). Hypotension, pain, irritability, facial/peripheral edema, lymphadenopathy, malaise, arthralgia and myalgia were also present. 29% of the patients (N = 9) had eosinophilia (> 500/mm³ cells); other accompanying laboratory anomalies are shown in Supplementary Table 1. The average elapsed time between

the onset of rash and performing the biopsy was 18.8 ± 28.3 days (range: 1-150 days). DIF analysis showed immune deposits in 19.4% (N = 6) of the patients; whereas no immune deposits were detected in 80.6% (N = 25) of the patients. The final diagnoses of the underlying cutaneous diseases were classified as 'category 1 (ABSD)', 'category 2 (ACDE)', 'category 3 (vascular skin diseases)' and 'category 4 (miscellaneous)'. Category 1 consists of bullous pemphigoid, pemphigus foliaceus; category 2 consists of ACDEs including SJS/TEN spectrum, DRESS, MDE, AGEP (acute generalized exanthematous pustulosis), fixed drug eruption, vasculitic

Table 1. Underlying etiologies of erythroderma and direct immunofluorescence findings.

| | Number of Patients N (%) | Presence of any accompanying bulla, vesicle pustule, erosion, crusting or necrosis | Direct Immunofluorescence Findings | Total (N, %) |
|--|-----------------------------|--|---|--------------|
| Category 1 (Autoimmune bullous skin disorders) | | | | 3 (9.7%) |
| Bullous Pemphigoid | 2 (2.9%) | Bulla, crusting and erosion | Linear IgG and C3 deposition at the dermoepidermal junction | |
| Pemphigus Foliaceus | 1 (1.4%) | Flaccid bulla, vesicle and crusting | Intercellular IgG deposition | |
| Category 2 (Adverse Cutaneous Drug Eruptions) | | | | 20 (64.5%) |
| Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis | 4 (5.8%) | Erosion, crusting and Nikolsky (+) bulla | None | |
| Maculopapular drug eruption | 10 (14.5%) | - | Only one patient had linear IgM, granular IgG and IgA deposition at the dermoepidermal junction | |
| Drug rash with eosinophilia and systemic symptoms | 3 (4.3%) | - | None | |
| Vasculitic drug eruption | 1 (1.4%) | - | None | |
| Fixed drug eruption | 1 (1.4%) | Bulla, erosion, crusting | None | |
| Acute generalized exanthematous pustulosis | 1 (1.4%) | Pustule | None | |
| Category 3 (Vascular Skin Diseases) | | | | 3 (9.7%) |
| Purpura Fulminans | 1 (1.4%) | Hemorrhagic bulla, necrosis | None | |
| Antiphospholipid syndrome | 1 (1.4%) | Hemorrhagic bulla, necrosis | None | |
| Leukocytoclastic vasculitis | 1 (1.4%) | - | None | |
| Category 4 (Miscellaneous) | | | | 5 (16.1%) |
| Mycosis fungoides | 1 (1.4%) | Bulla | Interrupted C3 deposition along dermal vessels and dermoepidermal junction | |
| Psoriasis | 1 (1.4%) | - | None | |
| Psoriasiform dermatitis (finally diagnosed as idiopathic erythroderma) | 1 (1.4%) | Pustule | Linear C3 deposition at the basal membrane | |
| Systemic allergic contact dermatitis | 2 (2.9%) | - | None | |

drug eruption; category 3 encompasses purpura fulminans, antiphospholipid syndrome and leukocytoclastic vasculitis, whereas category 4 consists of miscellaneous causes of erythroderma including, bullous mycosis fungoides, SCD, psoriasis and psoriasiform dermatitis (Table 1). Patients in category 3 (purpura fulminans, antiphospholipid syndrome and leukocytoclastic vasculitis) were accepted to present an erythrodermic-purpuric form of the disease described, since >90% of the body surface area were covered with erythema accompanied by hemorrhagic bullae and ecchymotic plaque. The most frequent final clinical-pathological diagnosis was ACDE category (category 2) (64.5 %, N = 20) followed by bullous pemphigoid (6.5%, N = 2) and SCD (6.5 %, N = 2) (Table 1). The only patient diagnosed histopathologically with 'psoriasiform dermatitis' was accepted to have an idiopathic form of erythroderma. Clinical and histopathological pictures of erythrodermic patients with different underlying etiologies are shown in Figures 1-5. Presence of any accompanying pustule, bulla, vesicle, necrosis, erosion and crusting were also determined as the part of dermatological examination as shown in table 1. For the category 2, the mean elapsed time between the onset of the rash and most probable inciting drug intake was 14.6 ± 13.9 days (range: 0-42 days). The most common probable causes of erythroderma were antimicrobials (40%, N = 8), followed by allopurinol (20%, N = 4), phenytoin (15%, N = 3), hydroxy-chloroquine (10%, N = 2), intravenous contrast media (10%, N = 2), chemotherapy agents (10%, N = 2) and others (15%, N = 3). The sample tissue for DIF examination was taken

from the intact skin just at the periphery of a bulla that had a pre-diagnosis of bullous pemphigoid or pemphigus foliaceus, whereas skin samples were obtained from a vesicle, bulla or pustule for the subjects who had pre-diagnosis of vasculitis or drug eruption. All 3 cases of erythrodermic patients in the category 1 diagnosed with either bullous pemphigoid (N = 2) or pemphigus foliaceus (N = 1), 1 patient from category 2 diagnosed with MDE and 2 cases from category 4 diagnosed with bullous mycosis fungoides and psoriasiform dermatitis, respectively, showed positive immunofluorescence in DIF assay. Two cases of bullous pemphigoid showed linear IgG and C3 deposition at the dermoepidermal junction (Figure 4), whereas intercellular IgG deposition was detected in pemphigus foliaceus.

Conclusions

To our knowledge, this is the first study which evaluates diagnostic significance of DIF examination in clarifying the etiopathogenesis of exfoliative dermatitis. Immunofluorescence microscopy is a well-developed, advanced technique which is utilized for the detection of tissue-fixed antibodies. For cutaneous disorders, DIF is used for designation of the antibodies bound to a specific antigen in the skin [7]. DIF assay simply involves the application of fluorescein-labeled secondary antibodies to a frozen section of sample tissue followed by examination of the issue for the deposition of immune reactants under immunofluorescence microscopy [7]. DIF is generally considered to be an auxiliary tool which aids

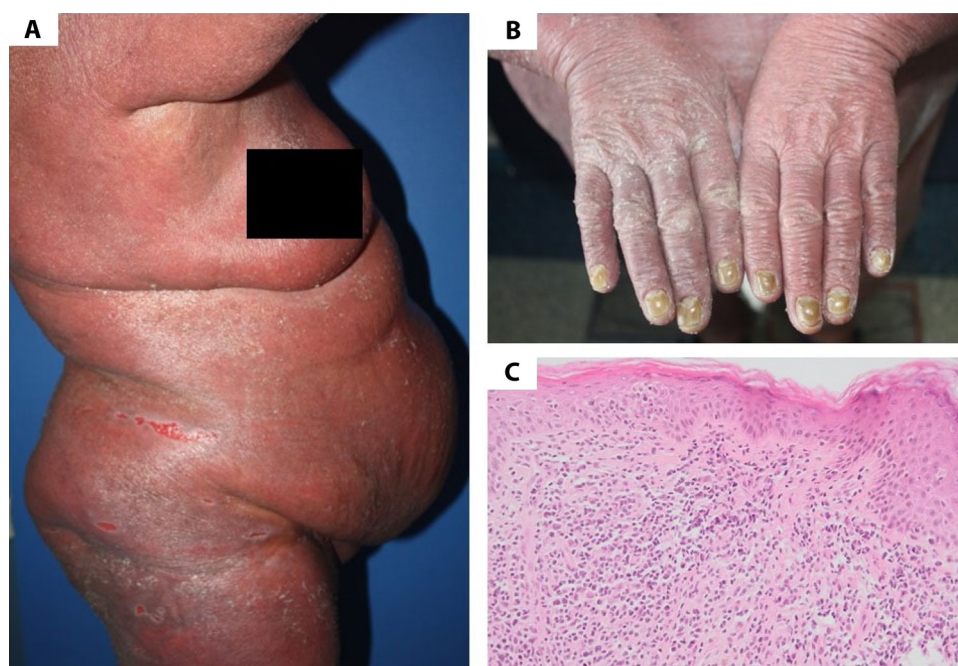


Figure 1. (A) Presentation of erythroderma in a patient diagnosed with mycosis fungoides widespread erythema and scaling. (B) Yellow/brown color change and subungal hyperkeratosis of the fingernails. (C) Diffuse dermo-epidermal atypical lymphoid infiltrate which shows epidermotropism (H&E, x200).

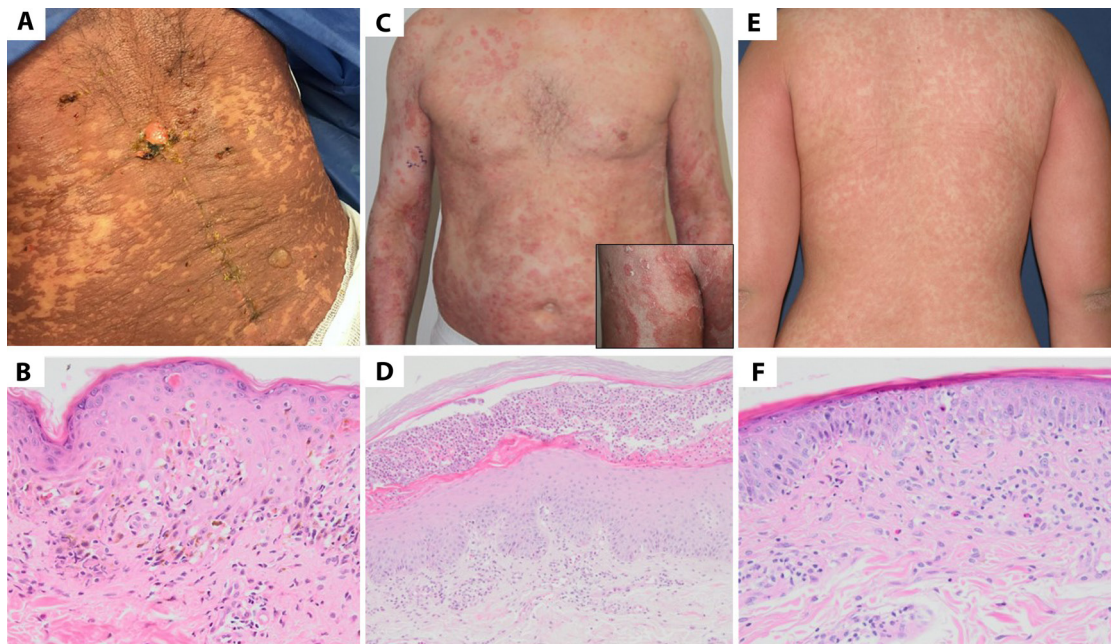


Figure 2. (A) Dusky red, violaceous targetoid plaque and bulla formation in a patient with SJS. (B) In the same patient skin biopsy, vacuolar degeneration, necrotic keratinocytes and pigment incontinence compatible with Stevens-Johnson syndrome are observed (H&E, x200). (C) Widespread annular, polycyclic-erythematous plaques with scale involving the trunk and the extremities, (inset) closer view of the plaques in a patient finally diagnosed with idiopathic erythroderma. (D) Histopathological examination of the patient revealed psoriasiform dermatitis with sub-corneal pustule formation (H&E, x200). (E) Widespread erythematous, confluent patches and plaques on the trunk in a patient with drug eruption. (F) The same patient's skin biopsy showed vacuolar degeneration at the basal layer, capillary congestion and perivascular eosinophilic and neutrophilic inflammation compatible with drug eruption.

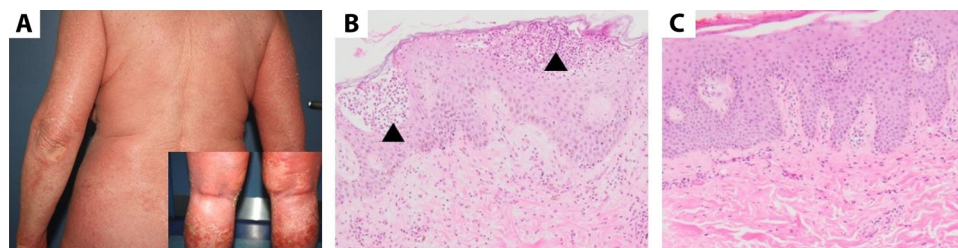


Figure 3. (A) Erythroderma in a patient with psoriasis. Histopathological findings in an erythrodermic patient diagnosed with psoriasis. (B) Subcorneal neutrophilic pustule (Kogoj pustule) formation is seen (arrowhead, H&E, x100). (C) Hypo-granulosis and psoriasiform acanthosis are present (H&E, x100).

to reach the accurate diagnosis of various dermatologic disorders especially when supportive histopathological changes are minimal. In dermatology practice, incorporating DIF findings with routine pathological findings are particularly useful in the patients pre-diagnosed with ABSD, connective tissue diseases and cutaneous vasculitis [7]. A study by Buch et al showed that the sensitivity of DIF was 94.44% and 84% in the pemphigus vs bullous pemphigoid group respectively [8]. DIF was shown to have diagnostic significance in the classification of cutaneous small vessel vasculitides especially in IgA vasculitis and lupus vasculitis [9]. In erythrodermic patients, expeditious diagnosis of the underlying cause is the essential step which enables the accurate intervention.

In our study, we aimed to determine the diagnostic utility of DIF in patients with exfoliative dermatitis.

Erythroderma appears to affect men more than women even though in some studies no sex predilection is showed [3,10]. In line with the present data in the literature, our study also showed a slight male predominance with a male-to-female ratio of 1.07. The mean age of affect study subjects in our study was 54.6 ± 23 years (range: 3- 86 years, median: 61 years). In a retrospective study of 49 erythrodermic patients, the average age was reported to be 50.7 ± 17.9 years which was in concordance with our findings [4]. As an acquired-adulthood disease, erythroderma may have various underlying etiologies or may be idiopathic in at least 25% of

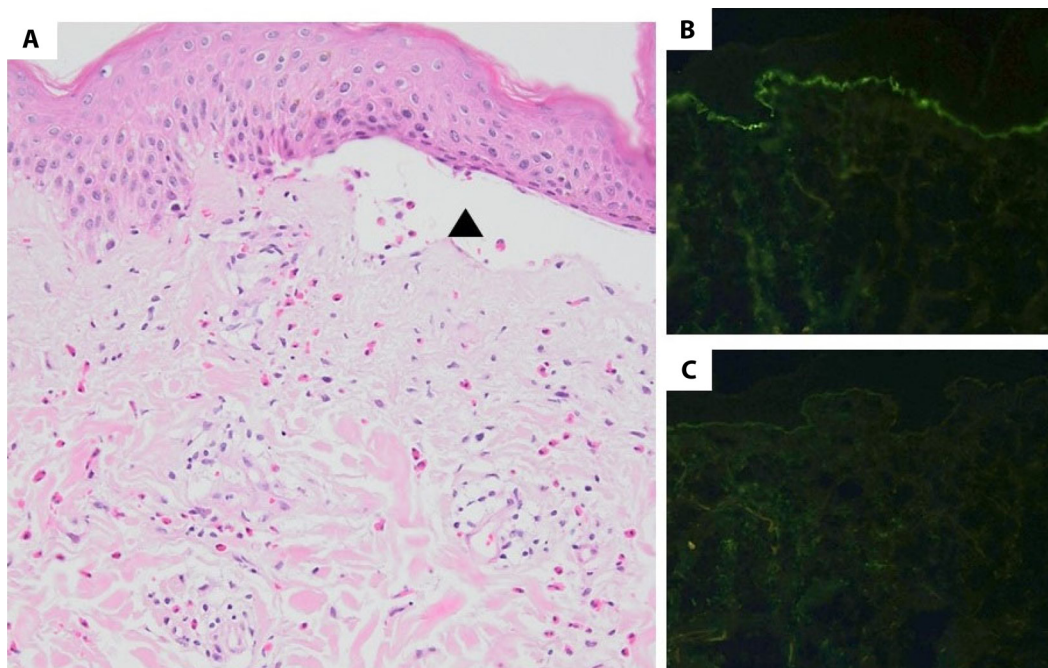


Figure 4. (A) Histopathological findings in an erythrodermic patient with bullous pemphigoid: sub-epidermal cleavage (arrowhead), eosinophilic spongiosis, superficial dermal edema and interstitial eosinophilic infiltration (H&E, x200). DIF revealed linear (B) C3 and (C) IgG deposition at dermoepidermal junction (DIF, x200).

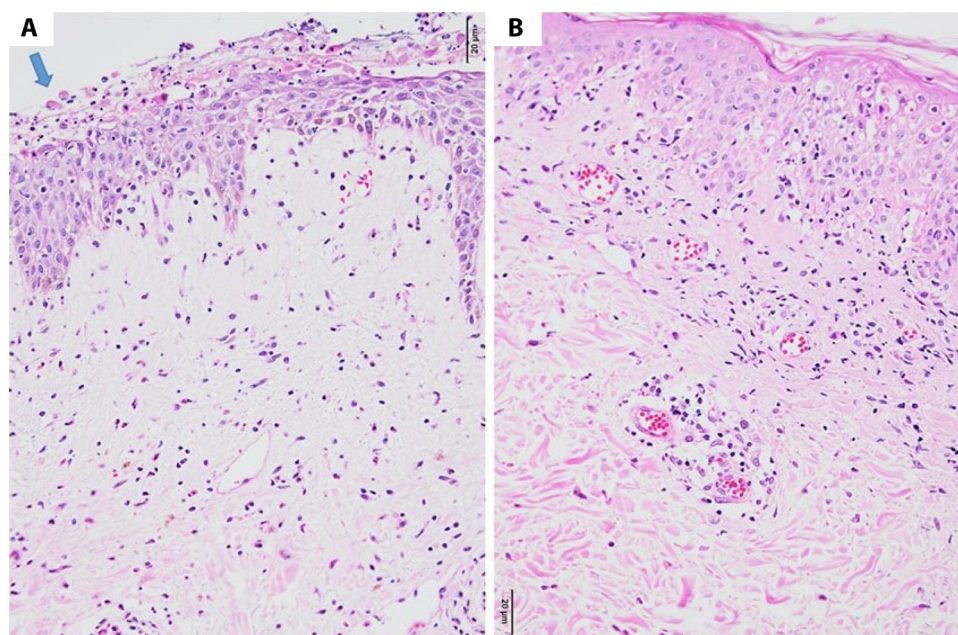


Figure 5. (A) Subcorneal/intragranular blister formation with neutrophils and few acantholytic cells (arrow). Dermal edema with mixed cellular infiltrate bearing eosinophil leukocytes (H&E, x200). (B) Basal cell vacuolization, spongiosis, necrotic keratinocytes, and lymphocyte exocytosis in the epidermis. Lymphohistiocytic inflammation and a few extravasated erythrocytes in the dermis (H&E, x200).

the cases [11]. In the present study, the most frequent underlying etiology of erythroderma was ACDE followed by ABSD, SACD, psoriasis and mycosis fungoides. In two patients with diagnoses of mycosis fungoides and psoriasis, generalization/ accentuation of the pre-existing dermatoses had evoked the erythrodermic status. In different studies, the most common diseases associated with erythroderma were pre-existing

dermatoses leading causes being psoriasis, eczema and atopic dermatitis, in contrast to our study [4,12,13]. In our retrospective study, we only included erythrodermic patients with available DIF examination results: this factor might explain the discrepancy between the results of our study and other ones. Our results show that skin samples for DIF examination were mostly taken from the patients with a suspected

diagnosis of bullous/vesicular or vasculitic skin diseases such as bullous pemphigoid, SJS, AGEP, FDE and leukocytoclastic vasculitis etc. So we most likely missed other causes of erythroderma for which DIF analysis was not performed in our center, which could be considered as a selection bias which is the limitation of our study.

In ACDE category, the most common causes of cutaneous eruption were antimicrobials followed by allopurinol, phenytoin, hydroxychloroquine, intravenous contrast media, chemotherapy agents and others. In concordance with our results, anticonvulsants, beta-lactams, allopurinol, rifampicin, trimethoprim-sulfamethoxazole and non-steroidal anti-inflammatory drugs are reported to be the leading causes of acquired erythroderma in multiple studies [4,13]. Only one patient in the ACDE group with a diagnosis of MDE showed deposits of linear IgM, granular IgG and IgA deposition at the dermo-epidermal junction. We believe that this immunoreactant deposition which was observed only in one patient was most likely non-specific. Duhra et al reported a case of paracetamol-induced fixed drug eruption with intercellular deposition of IgG and C3 in the lesional skin and suggested that immunoreactant deposition only in the affected skin might play a role in the recurrence of the lesions at the same site after a particular drug intake [14]. We want to underline the fact that MDE is a common cause of erythroderma and negative DIF examination favors the diagnosis of MDE, when ABSDs, fixed drug eruption and drug-induced vasculitis. In addition, two cases of TEN were shown to exhibit diffuse homogeneous deposits of IgM, IgA, IgG, C3c and C1q in the mid-epidermis of perilesional skin which was linked to the capacity of necrotic keratinocytes to absorb immunoreactants [15]. Diffuse intraepidermal deposition of immune deposits was thought to favor the early diagnosis of TEN [15]. In contrast with this report, we did not observe any immune deposition in 4 patients with a final diagnosis of SJS-TEN.

Overall, 6 (19.4%) patients showed immune deposition in DIF evaluation. All 3 cases of erythrodermic patients diagnosed with ABSDs had positive immunofluorescence in DIF assay. One patient was diagnosed to have pemphigus foliaceus; whereas the final diagnosis for the 2 patients was bullous pemphigoid. One patient diagnosed with MDE and two cases diagnosed with bullous mycosis fungoides and psoriasiform dermatitis, respectively showed positive immunofluorescence in DIF assay. Grekin et al reported 2 cases of erythrodermic psoriasiform pemphigus foliaceus which showed intercellular IgG deposition in DIF examination just like our study subject [16]. Our patient had presented with erythroderma accompanied by thick/adherent scales, superficial erosions and scattered hemorrhagic crusts resembling seborrheic dermatitis and SJS. Histopathological examination showed sub-corneal/intra-granular blister

formation with neutrophils and few acantholytic cells which was compatible with pemphigus foliaceus (Figure 5). With the aid of DIF examination which revealed intercellular IgG deposition, the diagnosis of pemphigus foliaceus was confirmed. On the other hand Joly et al reported three black African men diagnosed with lichenoid erythrodermic bullous pemphigoid [17]. In these patients, histopathological examination showed subepidermal bulla with lichenoid infiltrate along with linear deposits of C3 along the basal membrane.¹⁷ Two erythrodermic patients in our study presented with widespread intact/flaccid bullae, erosion and crust formation. Histopathological examination revealed sub-epidermal bulla, basal vacuolar degeneration and eosinophil-rich infiltrate. With the help of DIF analysis which detected linear deposits of IgG and C3 along the dermo-epidermal junction; the final diagnosis was bullous pemphigoid; the etiology of exfoliative dermatitis was unraveled.

In the category 4, the study subject with a final diagnosis of bullous MF showed interrupted C3 deposition along dermal vessels and dermoepidermal junction in the perilesional skin, whereas the case with the histopathological diagnosis of psoriasiform dermatitis and final clinical diagnosis of idiopathic erythroderma showed linear C3 deposition at the basal membrane in the perilesional skin. We believe that these C3 deposition are non-specific, thus does not seem to carry any diagnostic significance as reported in a study by Leibold et al [18]. In this study, 41 non-lesional, sun-exposed skin samples obtained from Mohs surgery sites, 21 specimens demonstrated interrupted, weak linear or granular staining with IgM, IgG, IgA, Clq and C3 antisera [18]. On the other hand, the two other patients with final diagnoses of leukocytoclastic vasculitis and vasculitis drug eruption did not show any immune deposition which might be linked to the long elapsed time between the onset of rash and biopsy (14 days) for both cases. DIF analysis is suggested to be performed within the first 24 hours to yield the best result [19]. Immunoreactants can not be shown efficiently 24-48 hours after the lesion formation.

Even though our study has limitations, in that it was a retrospective study and only small number of erythrodermic patients who had undergone both histopathological examination and DIF analysis were included, we would like to underline that DIF assay may be used as an auxiliary tool in enlightening etiopathogenesis of exfoliative dermatitis.

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