Erythema Elevatum Diutinum: A Neutrophilic Dermatosis Presenting as Bullae

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Case Report

Keywords: erythema elevatum diutinum, blister, leukocytoclastic vasculitis, bullous

Posted Date: April 6th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-386266/v1

Abstract

Background: Erythema elevatum diutinum (EED) is a rare disease that is associated with streptococcal infection, blood disorders, and autoimmunity. It is a chronic inflammatory dermatosis in the spectrum of cutaneous leukocytoclastic vasculitis. Typical skin lesions include nodules, erythema, and plaques; however, the presence of blister lesions is rare, especially on the limbs.

Case presentation: We report a rare case of EED that presented as blisters on both limbs and the trunk of a 62-year-old woman. She responded well to oral corticosteroid and hydroxychloroquine treatment. The lesions were significantly improved after 2 weeks of treatment.

Conclusions: EED is a rare form of cutaneous vasculitis. It is a good mimic of other types of skin diseases because of its diverse clinical presentations. It can even rarely present as blisters.

Introduction

Erythema elevatum diutinum (EED) is a chronic and rare form of cutaneous leukocytoclastic vasculitis. It was first described by Hutchinson in 1888 who reported that EED presented as violet to red-brown papules or nodules localised on extensor joint surfaces (1). Histologically, the early stage is characterised by a dense neutrophilic infiltrate with fibrinoid necrosis involving the papillary dermis and mid-dermal vessels, whereas the later stages involve dermal angiocentric fibrosis. EED has been associated with infectious and autoimmune diseases, such as IgA monoclonal gammopathy, leukaemia, lymphoma, human immunodeficiency virus, streptococcal infection, hepatitis B, celiac disease, inflammatory bowel disease, rheumatoid arthritis, cryoglobulinemia, systemic lupus erythematosus, and other neutrophilic dermatoses (2). Although their mechanisms remain elusive, bud antineutrophil cytoplasm antibodies and IgA have been recommended as diagnostic markers for EED (2). Atypical manifestations of the bullous form of EED are rare and have been most frequently observed on patients with human immunodeficiency virus (3, 4). We report a rare case of EED that presented as blisters intermingled with red-purple plaques on the extremities and trunk without underlying disease.

Case Presentation

A 62-year-old woman sought consultation for limb rash and pain. The rash on both feet lasted for 10 years and presented as soybean-size, reddish-brown papules and nodules. No significant improvement was noted despite treatment at several hospitals. However, topical application of glucocorticoid ointment improved her symptoms. The rash gradually extended to the limbs and trunk and merged with plaques and bullae, especially on the distal limbs (Fig. 1a-d). Increasingly obvious pustules and pain developed over the next 3 months. However, she claimed that annual health examination results did not reveal systemic diseases or tumours. Clinical differential diagnoses were Sweet syndrome, allergic vasculitis, erythema multiforme, bullous lichen planus, Kaposi sarcoma, bacillary angiomatosis, granuloma annulare, drug eruption, and bullous pemphigoid.

On physical examination, well-defined oedematous erythema was observed on the back of the hand and on the trunk. Dense, tight bullae and vesicles with a negative Nikolsky sign were distributed bilaterally on the lower extremities (Fig. 1d). Ophthalmic and superficial lymph node examination results were normal. The results of serological tests, including full blood count, blood glucose, liver and kidney function, anti-nuclear antibodies, human immunodeficiency virus antigens, and serum complement C3 and C4, were negative. A skin biopsy sample from the hand revealed swollen epidermis leukocytoclastic vasculitis, massive neutrophilic nuclear debris, and discrete extravasation of erythrocytes (Fig. 2a-d). The clinical features and pathology supported the diagnosis of EED. The lesions significantly improved after 2 weeks of 16 mg methylprednisolone and 400 mg hydroxychloroquine per day (Fig. 3a-b).

Discussion

EED is a rare cutaneous leukocytoclastic vasculitis involving the papillary dermis and mid-dermal vessels that results in a dense neutrophilic infiltrate with fibrinoid necrosis. Its diverse manifestations make early diagnosis extremely challenging. Although typical cutaneous lesions at atypical sites or atypical cutaneous lesions at typical sites have been reported (5), EED rarely presents itself as blisters, especially on the limbs and trunk. We reviewed the literature regarding variants that presented as blisters (**Table 1**) (4, 6-9). Cases presenting as vesicles (pustule or not) that underwent direct immunofluorescence were excluded. We observed that the histopathological presentation of EED with bullae comprised subepidermal blisters. Direct immunofluorescence test results were not

relevant or diagnostic of EED; however, they were important for diagnosing autoimmune bullous disorders. There have been 16 reported cases of vesicles, and almost all of them were pathologically manifested as epidermal vesicles.

Our current case presented as blisters with a transparent area that formed under epidermal oedema; however, they were not bullous. One of the mechanisms of blister formation is the release of enzymatic granules from neutrophils, resulting in alterations of the basal membrane (10). We inferred that the blisters on the lower limbs were subepidermal blisters due to the negative Nikolsky sign. We determined that the blisters formed during the acute phase because of the intense inflammatory response that occurs; this response is different than the pseudovesiculation of papillary dermal oedema that occurs during the early stage of EED. Because the characteristics of cutaneous lesions appear to mimic Sweet's syndrome, the diagnosis is challenging to pathologists. However, it has been reported that the bullous type of Sweet's syndrome is more prone to epidermal blisters. Although Sweet's syndrome and EED are related clinical entities in the spectrum of neutrophilic dermatosis (11), bullous EED should be considered as the differential diagnosis of bullous diseases.

Various hypotheses regarding the pathogenesis of EED remain unproven. Paraproteinaemia is strongly associated with EED (11) , but no causative relationship has been established. We performed an evaluation to determine the presence of immunoglobulin in the blood and found no evidence of paraproteinaemia.

Treatment with 16 mg methylprednisolone daily and 200 mg hydroxychloroquine twice daily for 2 weeks significantly improved the lesions. Dapsone was not used because the patient declined the glucose hexaphosphate dehydrogenase test. Both hydroxychloroquine and glucocorticoids are recommended as second-line medications for the treatment of EED, but such anti-inflammatory regimens should be encouraged. This combination was significantly advantageous for our case, resulting in rapid symptom improvement and recurrence prevention.

In conclusion, EED is a chronic condition with a diverse clinical presentation involving the face, extremities, and trunk. In rare cases, EED can present as a blister that pathologically manifests itself as a subepidermal blister.

Abbreviations

EED: Erythema elevatum diutinum;

Declarations

Consent form: All the authors agreed to publish in the journal of Diagnostic Pathology.

Funding sources: None.

Acknowledgement: None.

Conflicts of interest: none to declare.

Ethical information: The patient provided consent for publication of the case findings and images.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Tables

Table 1. Clinical features of erythema elevatum diutinum presenting as blisters

Reference	Patient age/sex	Site of involvement	Type of lesion	Type of bullae	Associated	DIF	Treatment
Tomasini et al	9 y/F	Extensor aspects of the extremities	Vesicles and bullae intermingled with red-purple papules and plaques	Subepidermal blisters	Pharyngotonsillitis	Negative	Sulphone and tonsillectomy
Chandrasekaran et al (7)	50 y/M	Extremities	Skin-coloured and erythematous nodules	Dermal papillary microabscess	Dermatitis herpetiformis	IgA deposits	Dapsone
Wang et al (8)	5 y/M	Face, trunk	Pruritic-scattered erythema, papules, blisters, blood blisters	Subepidermal blisters	None	Negative	Glycyrrhizin and indomethacin
Ossorio-García et al (4)	16 y/M	Dorsal surface of the hands	Symmetrical nodular lesions accompanied by vesicles	Vesicle of subepidermal origin	None	IgA deposits	No treatment
Gómez Arias et al (9)	60 y/M	Extremities, trunk, face	Denuded and crusty red-brown plaques, ulcerations	Subepidermal blisters	IgA monoclonal gammopathy, dyslipidaemia	Negative	Dapsone

DIF: Direct immunofluorescence; M: male; F: female.

Figures

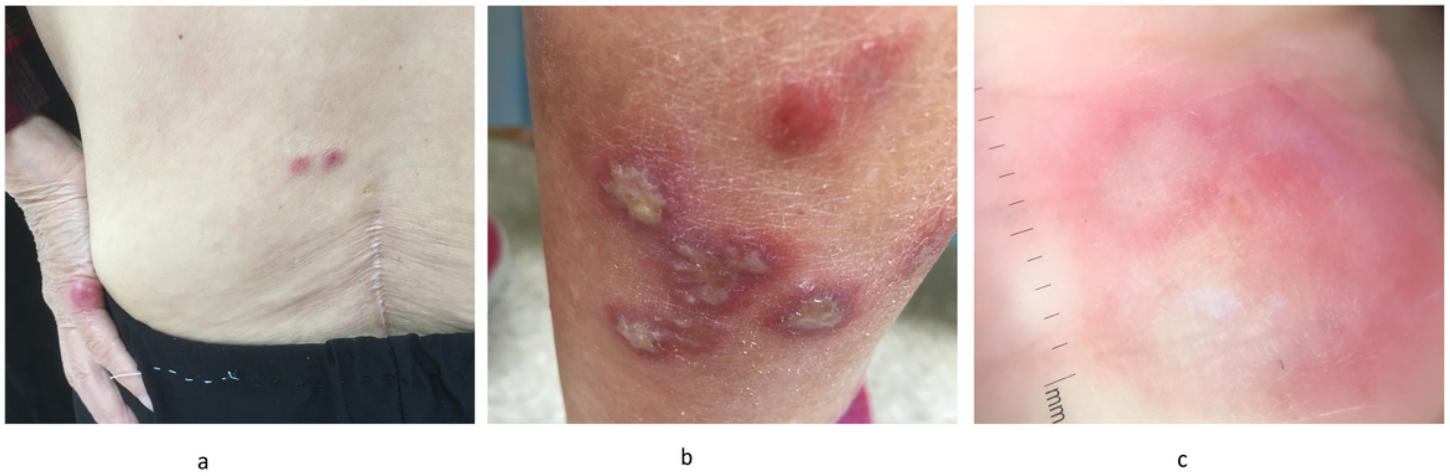

Figure 1

Clinical picture. (a) Physical examination revealed oedema and erythema on the hands and torso. (c) Bullae and pustules of the lower extremities. (d) A portable dermoscope was used to observe oedema and erythema of the hand (non-polarised light; original magnification ×10).

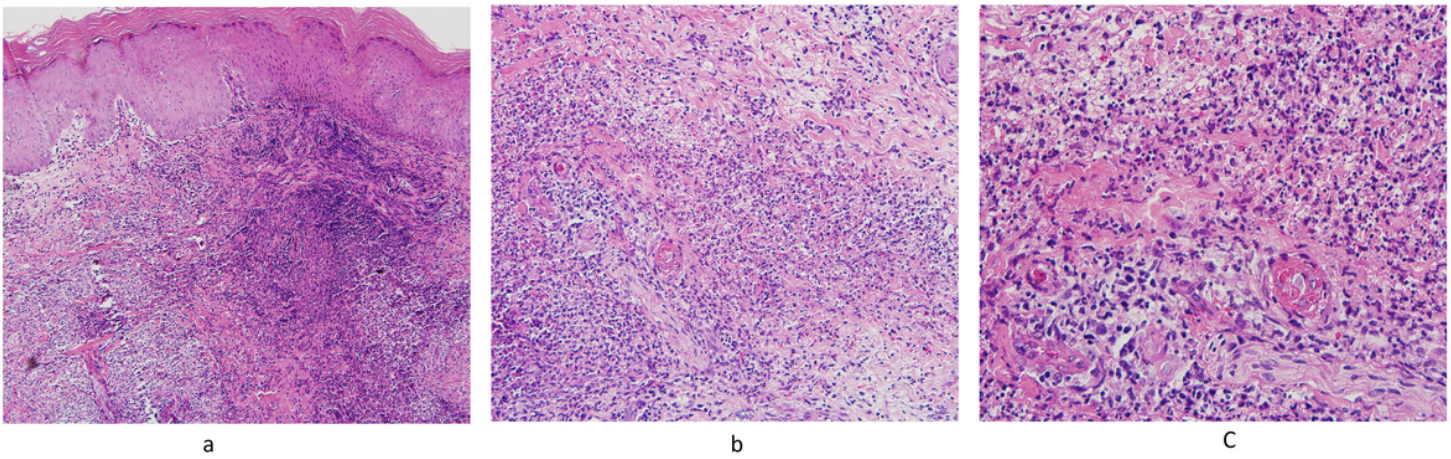

Figure 2

Histopathology. (a) The epidermis is highly oedematous and free of red blood cells (haematoxylin and eosin staining; original magnification ×100). (b) Diffuse cellulose exudation, neutrophil infiltration, and onion skin-like fibrosis surrounding the vessels (haematoxylin and eosin staining; original magnification ×200). (c) Histological findings were diffuse neutrophil infiltration and nuclear dust (haematoxylin and eosin staining; original magnification ×400).

Supplementary Files

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- After2weeksoftreatment.jpg