Diagnostic and therapeutic challenges in erythema elevatum diutinum

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ABSTRACT

Introduction: Erythema elevatum diutinum (EED) is a rare form of cutaneous fibrosing type of leukocytoclastic vasculitis leading sometimes to nodule formation, imitating neoplastic process.

Case report: We present the case of a 65-year-old woman with a 6-year history of cutaneous presentation of erythema elevatum diutinum, coexisting with myasthenia gravis and monoclonal IgA gammopathy. Dermoscopy of the skin lesions showed prominent thick arborizing vessels in a concentric alignment. Previous treatment with the use of methotrexate, dapsone, mycophenolate mofetil and cyclosporine did not stop the disease progression. Laboratory tests showed the presence of monoclonal protein IgAk in the serum and X-ray examination showed numerous fine-spot thinning of bone structure, especially within the skull bones. Hematological treatment with thalidomide and cyclophosphamide was introduced. A rapid resolution of skin lesions was observed.

Conclusions: This case shows that management of the underlying hematological abnormality may be essential for successful therapy of the otherwise treatment resistant erythema elevatum diutinum.

Key words: erythema elevatum diutinum, IgA monoclonal gammopathy, myasthenia gravis.

INTRODUCTION

Erythema elevatum diutinum (EED) is a rare form of chronic, recurrent, fibrosing type of cutaneous leukocytoclastic vasculitis. Cutaneous sequelae of acute inflammatory vasculitis in EED terminate with the formation of fibrous nodules. The disease may be associated with infectious, hematologic, rheumatologic or autoimmune diseases and neoplastic processes. High circulating level of antibodies formed in response to repeated infection and immune dysregulation mediated by associated conditions is suggested as underlying cause. The immune complexes created in the context of the paraproteinemia sustain the persistent local inflammatory infiltrate and the leukocytoclastic vasculitis.

OBJECTIVE

Herein, we report the case of 65-year-old woman with EED in association with IgA monoclonal gammopathy and myasthenia gravis in her past medical history. The patient had been treated with dapsone, doxycycline, mycophenolate mofetil, cyclosporine and by surgical excision with no response to the treatment and relapsing after surgery. When hematological treatment consisting of cyclophosphamide

and thalidomide was introduced, the disease started to regress.

CASE REPORT

65-year-old woman with a 6-year history of skin lesions and medical anamnesis of myasthenia gravis and monoclonal IgA gammopathy was admitted to our department in February 2020 for evaluation of her disease, EED and therapeutic interventions. The diagnosis of EED was established in 2017 based on the histopathological examination of the skin lesions. The patient presented gradually disseminating nodular tender lesions with accompanying pruritus since 2014. She was treated with methotrexate (20 mg/week) for 7 months, dapsone (100 mg/day) for 4 months, mycophenolate mofetil (4 g/day) for 3 months, cyclosporine (200 mg/day) for 6 months. There was no therapeutic effect after any of these drugs and nodular skin lesions were progressing. An attempt of surgical excision of the biggest nodules, has also been proven unsuccessful. Regrowth of the skin lesions at the surgical site has been observed. Her medical history revealed myasthenia gravis diagnosed in 2005 and IgA monoclonal gammopathy diagnosed in 2017.

On the physical examination firm reddish-brown disseminated nodules sized between 3 mm–8 cm were present symmetrically on the extensor surface of her upper and lower extremities and earlobes (fig. 1 A). In the dermoscopic image we have found two different compartments: the peripheral and the central one. The peripheral compartment included large, oval, ring-shaped, yellowish in color structures, located on the erythematous background and concentric root-like vessels (ginseng root), presented in both new and long-lasting lesions (fig. 2 A). Milky-pink areas with a different vascular component containing dotted, glomerular, and linear vessels, constituted the central compartment of the dermoscopic image (present predominantly in the long-lasting lesions) (fig. 2 B).

The skin biopsy of the early lesion revealed mid-dermal perivascular and interstitial mixed-cell inflammatory infiltrate composed of lymphocytes, monocytes and neutrophils, with nuclear "dust" of neutrophils, leukocytoclastic vasculitis, fibrin deposition within the vessel walls, extravasated erythrocytes and collagen degeneration of the reticular dermis corresponding to EED (fig. 3 A). The surrounding stroma showed fibrohistiocytic activation with many dilated blood vessels and myxoid stroma changes (fig. 3 B). In the fibrotic firm nodule surgically removed from the knee, diffuse dermal fibrosis was demonstrated (figs. 3 C, D). Vertically oriented vessels also favored EED.

Laboratory tests revealed decreased hemoglobin concentration, increased erythrocyte sedimentation

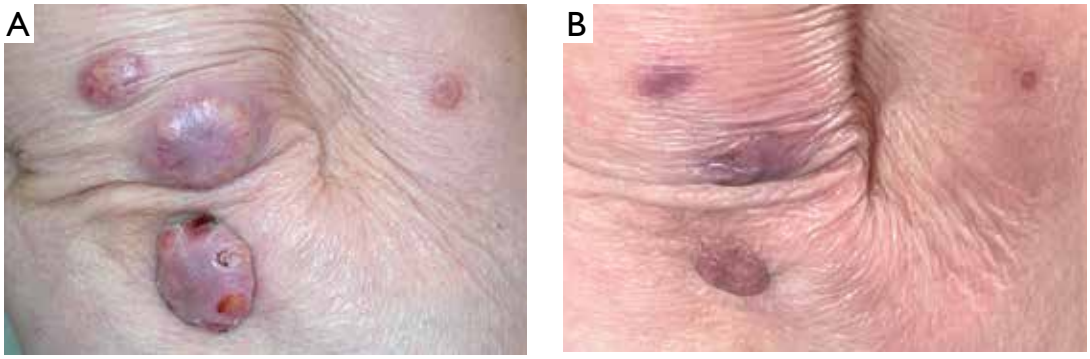

Figure 1. A – Several reddish-brown nodules located on the skin of the left elbow joint. Tender lesions were accompanied by itching. **B** – Skin lesions after 6 months of therapy with thalidomide and cyclophosphamide, leading to nodule regression and post-inflammatory discolorations

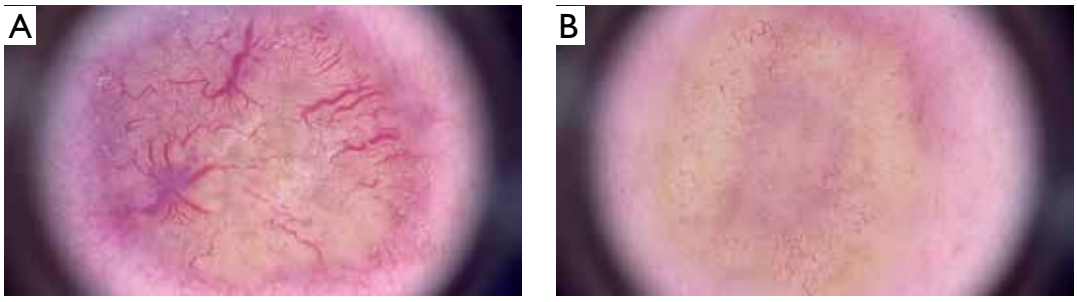

Figure 2. A – Dermoscopy of the early EED lesion: concentric root-like vessels (ginseng root) located on the erythematous background. **B** – Dermoscopy of the long lasting nodule of EED: peripheral large, oval, ring-shaped, yellowish in color structures; concentric milky-pink areas with a vascular component containing dotted, glomerular, and linear vessels

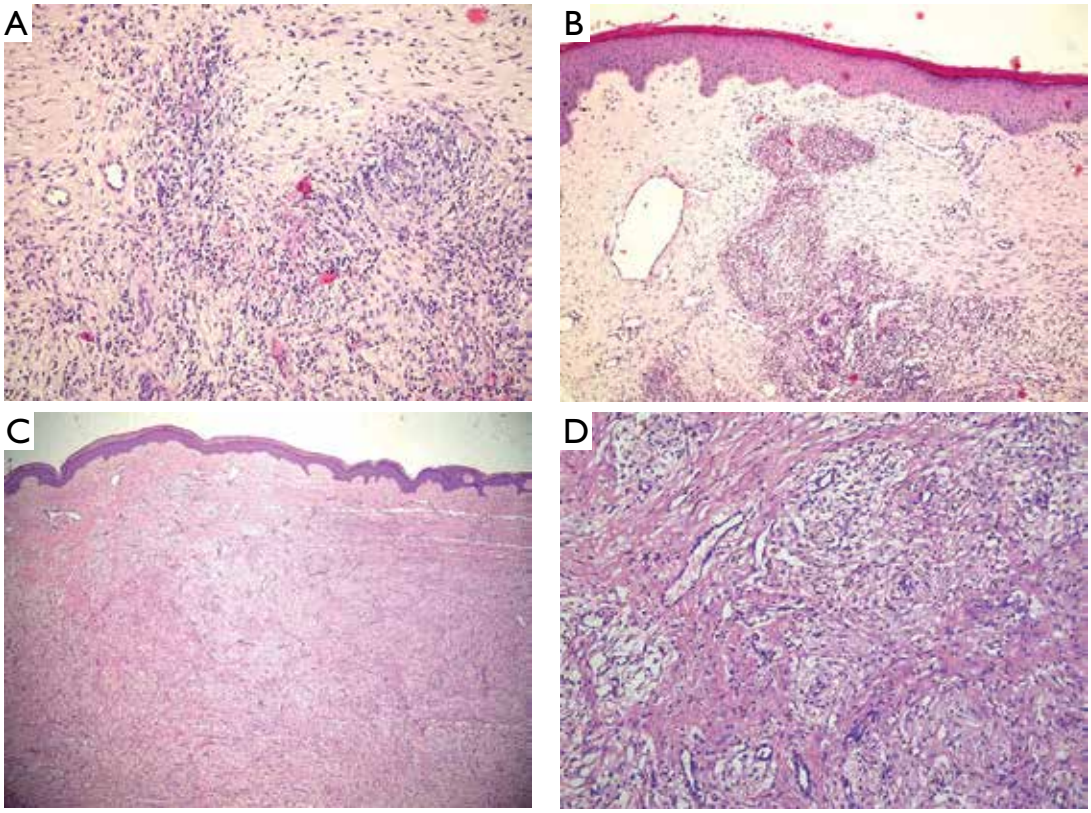

Figure 3. A – Histopathology of the early erythema elevatum diutinum demonstrating leukocytoclastic vasculitis. There is a diffuse dermal mixed-cell infiltrate in which polymorphonuclear cells predominate with leukocytoclastic debris and fibrin around and within the vessels' walls in the superficial plexus with extravasated erythrocytes around (H&E, 200×). **B** – At the periphery of the vasculitis, the dermis contains increased numbers of dilated blood vessels and myxoid connective tissue (H&E, 100×). **C** – The nodule of the advanced EED lesion showed fibrosis composed of spindled fibroblasts interspersed between reticular dermal collagen bundles. Dilated blood vessels are seen in the superficial dermis and are appreciated at dermatoscopy examination (H&E, 40×). **D** – Perivascular lamellar fibrosis with an onion-bulb-like pattern with hemosyderophages can be noticed indicating resolving vasculitis. Some vessels are dilated and contain hypertrophic endothelial cells projecting into the lumen. Interstitial neutrophilic inflammation with nuclear leukocytoclasia is seen between the collagen bundles (H&E, 400×)

rate, elevated levels of IgA immunoglobulin and β_2-mikroglobulin and the presence of monoclonal protein IgAk in the serum. X-ray examination of the skeleton showed numerous fine-spot thinning of the bone structure, especially within the skull bones. Due to progression of changes in the X-ray image compared to the previous photographs, it was decided to redirect the patient to the hematology department to establish hematological diagnosis and offer adequate therapeutic solution. Decision was made to include thalidomide and cyclophosphamide treatment. Chemotherapy due to monoclonal gammapathy was responsible for the resolution of the skin lesions (fig. 1 B).

DISCUSSION

EED is a rare form of cutaneous small vessel leukocytoclastic vasculitis with chronic and relapsing course associated with patterned dermal fibrosis. It has been shown that majority of EED cases are associated with hematologic, or autoimmune disturbances, or infectious causes characterized by prolonged course [1].

EED affects mainly adults with no gender nor racial predilection [1]. The clinical features include yellowish to red-brown papules, plaques and nodules typically located on extensor surfaces of the extremities, as well as on the buttocks, trunk and head [1] with symmetrical distribution. Pain or itch may be present.

Skin biopsy remains the method of choice to establish the diagnosis. The histopathological patterns in EED depend on the stage of the disease and include small-vessel neutrophilic vasculitis at the early stage of the lesions, progressing to perivascular and dermal fibrosis and extracellular lipid deposits at the later stage [2]. Sardiña *et al.* published a case of idiopathic EED, in which biopsy showed in addition to the typical features, an associated mixed inflammatory infiltrate, and prominent macrophage neutrophilic cytophagia with no clinical or serological compelling evidence of Sweet's syndrome [3]. The difficulties of differential diagnosis of the fully developed EED

in which nodular neutrophilic infiltrate with variable leukocytoclasis is present in Sweet's syndrome, palisaded neutrophilic granulomatous dermatitis (PNGD), and the bowel-bypass, the bowel-associated dermatosis-arthritis, and Behçet's syndrome are well known [4]. Giving the rarity of idiopathic cases, further investigation is needed to establish potential reproducibility of the pattern described by Sardiña.

Late stage EED mimics a fibroblastic tumors and has to be differentiated from fibroblastic and neural neoplasms [5]. Crucial for EED diagnosis regardless of its duration is diffuse neutrophilic inflammation, nuclear leukocytoclasia around the vessels and signs of vasculitis.

Direct immunofluorescence may reveal changes consistent with immune complex-mediated vasculitis, such as intravascular and perivascular fibrin deposits, accompanying with complement and immunoglobulins presence, including IgG, IgA or IgM [6].

Recently published paper by Tran TA. claims the subset of chronic localized fibrosing leukocytoclastic vasculitis (CLFLCV) to which EED belongs, might represent cutaneous manifestations of IgG4 related disease, especially when dermal storiform fibrosis is associated with IgG4-positive plasma cells infiltrate [7]. Clinical manifestation of IgG4-related localized chronic fibrosing vasculitis differs from EED in terms of location and presents as nodular dermatitis or subcutaneous nodule. The accurate diagnosis is crucial in the clinical management of patients with IgG4 sclerosing diseases. Therefore in case of fibrosing leukocytoclastic vasculitis with plasma cells infiltrate, the immunostaining with IgG4 should be considered [7].

In the case of chronic localized fibrosing leukocytoclastic vasculitis (CLFLCV) described by Carlson's group [8], the location associated with poor lymphatic drainage may be the underlying factor maintaining recurrent episodes of immune-complex vasculitis and progressive fibrosis leading to verrucous hard nodule or ulcerative plaque formation. Therefore solitary lesion with histopathological resemblance to granuloma faciale, such as eosinophilic-rich small-vessel neutrophilic vasculitis associated with storiform and angiocentric fibrosis may correspond to the paraneoplastic vasculitis, but also may represent a unique example of cutaneous inflammatory pseudotumor due to lymphatic drainage obstruction.

In our patient the clinical presentation corresponded to EED. Distribution of skin lesions was symmetrical. No lymphoedema was observed. There were no plasma cells visible in the lesional skin biopsies, and histopathological findings did not reveal eosinophilic-rich small vessels vasculitis.

Dermoscopic examination of the plaques and nodules of different time duration was performed.

The dermoscopic image is correlated with the histopathological examination. The large, oval, yellowish in color structures belonging to peripheral compartment correspond to myxoid stroma changes, while milky-pink areas present in the central part correspond to diffuse dermal fibrosis. Dotted vessels seen in the central compartment are described in the histopathology as vertically oriented vessels. The close correlation between dermoscopic and histopathological examination emphasizes the importance of dermoscopy in the diagnosis of EED lesions as a non-invasive method. The presence of concentric root-like vessels (ginseng root) corresponding to dilated blood vessels, may be highly diagnostic. Further studies are needed to establish the repetitive dermoscopic pattern of EED.

The literature regarding EED reports its association with hematological abnormalities such as myelodysplasia, multiple myeloma, lymphoma and paraproteinemia, in which primarily IgA gammopathy is the most frequent one [9].

Our case indicates that EED is not a distinct disease entity, but rather a clinicopathologic reaction pattern to IgA monoclonal gammopathy. Dapsone, mycophenolate mofetil and cyclosporine which are widely used in vasculitis treatment, were unsuccessful in our patient. Also, methotrexate utilized at the dose of 20 mg/week did not show any therapeutic benefit. From 4-year period of follow-up of the patient, the fact of progressing IgA hyperglobulinemia leading to osteolytic bone changes, presence of monoclonal protein IgA kappa in serum can be considered as the leading cause of EED chronicity and stimulant of leukocytoclastic vasculitis. MGUS (monoclonal gammopathy of undetermined significance) directed chemotherapy led to the regression of persistent skin lesions and inhibited the appearance of the new ones. Therefore in the treatment of unresponsive case of EED, the thorough screening for the underlying conditions is crucial.

CONCLUSIONS

The correct diagnosis of EED is important and subsequent work up for associated autoimmune processes, infectious causes and hematological abnormalities is recommended. Such diseases influence prognosis and treatment efficacy. In refractory cases of EED, treatment of the underlying disease may prove to be an appropriate way to obtain relief from EED symptoms.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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