

# ERITEMA ELEVATUM ET DIUTINUM AND THE TRIGGER FACTOR'S ROLE IN ITS PATHOGENESIS – CASE REPORT –

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**Abstract:** Eritema elevatum et diutinum (EED) is a rare form of leukocytoclastic vasculitis, with unknown etiology, whose onset could involve infections, autoimmune diseases or monoclonal gammopathy. We present the case of a female patient, who came with the recent onset of a rash that consisted of erythematous papules and nodules localized on the interphalangeal joints and thenar eminence, associated with local burn, pain and arthralgia in the small joints of the hands. Clinically, the lesions had a particular aspect, with inflammatory characteristics and abcedation tendency, which oriented the diagnosis towards EED. There were some differential diagnosis problems with other vasculitis. The histopathological exam confirmed the diagnosis of EED. In our case, there were multiple trigger factors such as bacterial and fungal infections, hepatitis with C virus and tuberculinic hyperergy.

**Cuvinte cheie:** eritema elevatum et diutinum, vasculită

**Rezumat:** Eritema elevatum et diutinum (EED) este o formă rară de vasculită leucocitoclastică, cu etiologie încă necunoscută, în apariția căreia ar putea fi implicați factorii infecțioși, bolile autoimune sau gammopatiile monoclonale. Relatăm cazul unei paciente, ce se prezintă pentru apariția relativ recentă a unei erupții eritemato-papulo-nodulare, dispuse simetric la nivelul articulațiilor interfalangiene și la nivelul emințelor tenare, însoțită de arsură locală, durere și artralgie la nivelul articulațiilor mici ale mâinilor. Clinic leziunile au avut un aspect particular, cu caracter inflamator și tendință la abcedare care au orientat cazul spre diagnosticul de EED, dar au pus probleme de diagnostic diferențial cu alte vasculite. Examenul histopatologic a confirmat diagnosticul clinic de Eritema elevatum et diutinum. În cazul nostru s-au evidențiat mulți factori triggeri infecțioși, respectiv bacterian și fungic, virusul HC și hiperergia TBC.

## INTRODUCTION

Eritema elevatum et diutinum (EED) is a vasculitis characterized by the formation of firm papules and nodules, with symmetrical distribution on the extension surfaces. The typical lesions have a red-violet or brown-reddish colour and can become confluent in plaques.(13)

The disease was initially described by Hutchinson in 1888 and later by Bury in 1889. The name of elevatum et diutinum was used for the first time by Radcliff-Crocker and Williams, who divided this condition in two groups: the type Bury, which has a tendency to appear in younger women with history of rheumatologic diseases, and the type Hutchinson with a tendency to appear in older men. Although described for the first time in the 19th century, the largest study that referred to this disorder was published in 1992 and included 13 patients.(5,11,28,29)

## CASE REPORT

We present the case of a female patient, aged 61, from the urban environment, who was admitted to the Dermatology Department of the Clinical Hospital of Sibiu with a recent onset (weeks) of pain-inducing inflammatory nodules. They were initially localized on the thenar eminence of the right hand and interphalangeal joints of the same hand, with extension on the left hand; the lesions were associated with arthralgia in the small joints of the hand. The patient was treated with oral antibiotics and local dermocorticoids without any improvement, even with the appearance of new lesions on the same areas.

The patient's medical history revealed that she has had chronic hepatitis with C virus, for which she followed treatment with Interferon and Ribavirine in 2008, followed by a complete sustained response.

The dermatological exam showed: symmetrical nodular inflammatory lesions of red-violet colour, firm, with relatively good demarcation, painful, and with a fluctuation tendency, smooth surface and little peripheral scales that were localized on the thenar eminence and on the skin of the interphalangeal joints (figures no. 1 and 2).

**Figure no. 1. Eritema elevatum et diutinum – the nodular lesions aspect on the hands before treatment**



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**Figure no. 2. Eritema elevatum et diutinum – the nodular lesions aspect on the hands before treatment**



The lab test showed: moderate biological inflammatory syndrome, VSH 13mm/h, pharyngeal exudates + for *E. Coli* and yeasts (*Candida*++), immunogram: small increase of IgA. Other investigations, liver exams, renal exams, electrophoresis, clotting tests - normal values, IDR for 2 PPD units: Palmer III/15 mm.

**Cutaneous biopsy:** cutaneous biptic fragment covered by acantolitic keratinized paved epithelium with little hyperkeratosis; dermo-epidermal junction well demarked with minimal exocytose. The superficial dermis vessels had hyperemia, in dermis there was a mixed inflammatory infiltrate with perivascular predomination that was formed by lymphocytes, polymorphonuclear neutrophils and eosinophils, plasmocytes and hystiocytes. Areas with leukocytoclasia and the formation of "nuclear dust", with nuclear fragments of the degenerated leukocytes and extravasated erythrocytes (with a leukocytoclastic vasculitis aspect) were also present. Some vascular lumens presented infiltration and dissociation of the vascular wall with polymorphonuclear neutrophils. There was little quantity of fibrin. The PAS staining showed the presence of fibrinoid necrosis.

The arguments that sustain the diagnosis of EED, in this case, are:

- The clinical aspect with symmetrical inflammatory nodules on the thenar eminence and the skin of the interphalangeal joints (dorsal face of the hand) associated with poliartalgias in the small joints of the hand;
- the histopathological aspect of vasculitic process with leukocytoclasia (perivascular infiltrate formed by neutrophils, with fragmented nuclei, forming the so-called "nuclear dust").

It would have been necessary to effectuate direct and indirect IF to show the immunoglobulin and complement deposits.

We initiated pathogenic treatment with metilprednisolon 32 mg/day; for the micro-bacterial infection of the oral cavity and the reduction of abcedation tendency we initiated oral antibiotherapy, in concordance with the antibiogram, antifungal treatment and local treatment with antiflogistic compresses and topical dermocorticoids, with favorable response.

With this treatment, the nodular lesions partially remitted, but with relapse tendency and the onset of new lesions. As a result, after we had the HP exam, we initiated the treatment with Dapsone 100mg/day (Disulone®).

### DISCUSSIONS

Eritema elevatum et diutinum (EED) is considered to be a discreet, chronic form of leukocytoclastic vasculitis.

The ethyopathogenesis of EED is not totally understood. The cutaneous lesions are considered to be produced by the circulant immune complex deposits in the small vessels. This factor activates inflammatory reactions, which affect the vessels. Repetitive deterioration of small vessels in the damaged areas could determine local fibrosis. In direct IF, one could observe complement deposits, as well as IgG, IgM, IgA and fibrin around the damaged vessels.(5,28)

EED is frequently associated with autoimmune diseases, such as rheumatoid arthritis, celiac disease, bowel inflammatory disease and type I diabetes mellitus.(2,4,8-11,14-18,20,22) Among the causes that can have a role in the onset of these diseases, we underline the following:

- Recurrent bacterial infections (especially streptococcal infections) (7), viral infections (including hepatitis B, C or HIV).
- Rheumatologic disease, erythematous lupus, B cell lymphoma (26,29)
- Monoclonal gammopathy, in particular with IgA, hematological disorders.(28)

A clinical and histopathological study in EED showed that the disease is associated with hematological disorders, in particular with monoclonal gammopathy with IgA, multiple myeloma, myelodysplasia. It has been showed that EED can be preceded by myeloproliferative disorders with an average of 7-8 years.(27)

The medical literature reported cases of EED that appeared after erythropoetin use (14), as well as others associated with peripheral ulcerative keratitis, an inflammatory disorder of the cornea that can either appear at the same time, or precede or succeed the onset of EED.(21,23,1) Peripheral ulcerative keratitis is frequently associated with systemic autoimmune disease.(12) In the majority of cases, we observed a favourable response in the skin lesions and in the ophthalmologic pathology after Dapsone administration.(14,23)

The differential diagnosis of the skin lesions must be made with other leukocytoclastic vasculitis:

Postmedication vasculitis – always superficial; the group of incriminating drugs includes: antibiotics with beta lactamic nucleus, sulphones, thiazidic diuretics, AINS, sleeping pills, tranquilizers.(19)

Vasculitis from infections – produced by CIC or endothelial lesions due to microbial toxins. In this case, the cutaneous lesions are associated with a systemic response: fever, shivers, altered general status. These types of vasculitis were described in streptococcal infections, staphylococcal infections, pneumonia, hepatitis (HBV).(19)

Vasculitis associated with other systemic disease: cryoglobulinemia (frequent in C virus hepatitis), hipergammaglobulinemia, lymphoproliferative and myeloproliferative neoplasia, congenital complement deficit.

Vasculitis from collagenosis – LES, dermatomyositis, Sjogren syndrome, reumatoid poliartiritis.(4,11,18)

Poliartiritis nodosa - affects medium and small calibre arteries, cutaneous lesions include palpable purpura, livedo reticularis, ulcerations and infarct of the fingertips, subcutaneous hemorrhage. Anatomopathologically, the skin lesions consist of necrotic inflammation of small and medium arteries, initially with polymorphonuclear neutrophils that affects entire thickness of the vascular wall and then fibrinoid necrosis, followed by granulation tissue formation. A HP characteristic is the fragmentation of internal elastic lamina.(24)

Other affections that must be excluded are the following:

- Pernio erythema–erythematous-edematous nodular lesions: coloured in red-violet, well demarked, with high local temperature, localized on the extremities, after exposure to

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- cold, in predisposed persons to peripheral vascular dysfunctions.
- Nodular tuberculids – painful, cyanotic nodular lesions characterized by an intense positive IDR to PPD and in the HP exam a nodular tuberculoid infiltrate (groups of epitheloid cells surrounded by a band of lymphocytes, with giant cells); no caseous necrosis and no Koch bacillus in the HP exam;
  - Cutaneous sarcoidosis - diffuse sarcoidosis, frequently localized on the back of the hands and fingers; it is present in prominent red-violet plaques, with firm or warty consistence, smooth glossy surface, yellow colour in vitropresure (lupoid sarcoids).The histopathological exam shows epitheloid cell follicle, well-demarcated, which presents giant cells with citoplasmatic inclusions (Schauman bodies) in the centre. The radiological image can show mediastinal adenopathy when it is associated with lymph nodes manifestations; a characteristic element is a negative IDR to PPD.
  - Annular granuloma - papular rash in an annular or half-round shape, frequently localised on the extremities, characterized in the HP exam by subcutaneous infiltrate with central collagen necrosis (eosinophilic aspect), surrounded by a “palisade-like” hystiocyte infiltrate with a peripheral inflammatory infiltrate.
  - Heberden nodules-appear in artrosis and represent, in fact, marginal osteophites in distal interphalagian joints; sometimes the onset is acute with erythema and pain in the affected joints;
  - Gout tophi - periarticular firm nodules, with secondary onset due to uric acid crystal deposits in articular and periarticular tissues.(4,11,18)

### Evolution and prognosis

As the name of the disease suggests, this disease has a chronic (diutinum=persistent) or intermitten outcome, lasting months or years. Lesions can evolve to spontaneous resorption in 5-10 years.(27)

The *quo ad vita* prognosis is good and depends on the systemic disease, *quo ad laborem* - with the possibility of restarting the daily activities in a matter of weeks, *quo ad sanationem* - with the possibility of cure, but also of relapse of the nodules, *quo ad functionem* - with compensation possibility, and from the aesthetic point of view, with a complete disappearance of lesions and only discreet hyper-pigmented atrophy.

### Treatment

Because of the possible side effects, before initializing the treatment and on long term therapy, it is necessary to make complete blood, hepatic and renal investigations. The first line systemic treatment consists of the administration of sulphones, particularly Dapsone (diamino-phenil-sulphone or Disulone) in an attack dose of 150 mg/day, followed by a reference dose of 50-100 mg/day for several weeks. The adverse reactions are on the hematological line (methemoglobinemia, hemolytic anemia that appears on 200-300 mg/day dose, agranulocytosis), gastrointestinal disorders (anorexia, nausea, vomiting), peripheral motor neuropathy, hepatic-renal toxicity. The systemic corticosteroids determine the resorption of cutaneous lesions, but with a relapse tendency.(4,5,11,18)

**Possible complications** that can develop: infection and ulceration of nodules, secondary nodules necrosis due to neutrophilic enzymes that have a destructive role in the vascular wall. The complications related to Dapsone administration are hematological (methemoglobinemia, hemolytic anemia, agranulocytosis) and neurological (peripheral motor neuropaty).(4,11,18)

Because of the fact that the skin lesions initially presented a marked inflammatory character with fluctuation tendency, with the presence of E. Coli and Candida, the infection's trigger role had to be taken into consideration, compelling us to initiate systemic antibiotherapy of first line. The initial favourable response, only after systemic antibiotherapy (without corticotherapy) pleads for the role of E. Coli infection in the onset and aggravation of EED .

In our case, another possible trigger factor for the pathogenesis of this disease could be the chronic C-virus hepatitis, even though at this time the patient has had a complete sustained response to the specific treatment with Interferon and Ribavirine.

The modified IDR to PPD (Palmer III/15) shows a tuberculinic hiperergy, but excludes the diagnosis of tuberculoid nodules through the HP exam, that showed a leukocytoclastic vasculitis. We must recall the role of subclinical TBC infection as a trigger of a cutaneous leukocytoclastic vasculitis process, since we know that tuberculosis can determine this kind of vasculitis.(6,15)

## CONCLUSIONS

Eritema elevatum et diutinum is a distinct, rare form of cutaneous leukocytoclastic vasculitis that can have differential diagnosis problems. Thus, the HP exam is of great importance, requiring a second or even a third opinion. The etiopathogeny of the disease is not completely eluded, but it is possible that repeated antigenic stimulation or an infection can play the key trigger role in its pathogenesis.

The case's particularity consists of an aspect of nodular lesions with a tendency of abcedation and the identification of associated infections as a trigger factor, showing a favourable response to antibiotherapy and corticotherapy, but only with the necessary association with Dapsone because of the coetaneous rash relapse tendency.

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## CLINICAL ASPECTS

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