

CLINICAL CASE

Intravenous immunoglobulin for treatment of severe acquired bullous epidermolysis refractory to conventional immunosuppressive therapy

Imunoglobulina intravenosa para tratamento de epidermólise bolhosa adquirida grave refratária a terapia imunossupressora convencional

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Abstract: Acquired bullous epidermolysis is a chronic and rare bullous subepidermal disease. It usually begins in adulthood and its etiology is unknown although it is associated with antibodies against type VII collagen. There are spontaneous and trauma induced formation of blisters that may cause serious complications. Treatment is disappointing and difficult. Apart from conventional therapy with systemic corticosteroid, new therapeutic modalities such as intravenous immunoglobulin are currently being used. This report highlights the extremely difficult clinical management of this rare disease and the important improvement provided by intravenous immunoglobulin.

Keywords: Acquired bullous epidermolysis; Immunosuppressive agents; Immunoglobulins, intravenous

Resumo: A epidermólise bolhosa adquirida é doença bolhosa subepidérmica crônica e rara. Geralmente, inicia-se na fase adulta, sendo a etiologia desconhecida, embora vinculada à presença de anticorpos contra o colágeno tipo VII. Há formação de bolhas, espontaneamente ou após trauma, podendo causar complicações graves. O tratamento é desapontador e difícil. Além da terapia convencional com corticoides sistêmicos, recentemente, novas modalidades terapêuticas promissoras estão sendo utilizadas, dentre elas, a imunoglobulina intravenosa. Destaca-se, neste relato, o difícil manejo clínico desta doença, e a melhora importante com a imunoglobulina intravenosa.

Palavras-chave: Epidermólise bolhosa adquirida; Imunoglobulinas intravenosas; Imunossupressores

INTRODUCTION

Acquired bullous epidermolysis (EBA) is a chronic and rare bullous subepidermal disease which develops on the skin and mucosas and that usually starts in adulthood.^{1,2} It has an incidence of 0,2 per million of people, regardless race or sex.³ There is association with allele HLA DR2, suggesting predisposition to EBA among carriers of this phenotype who are also more sensitive to bullous lupus.⁴ The etiology is unknown although it is associated with the pres-

ence of antibodies against type VII collagen, main structural component of the anchorage fibrils of the dermo-epidermic junction, that could lead to a decrease in the number of anchorage fibrils.² The skin is fragile, bullae are formed spontaneously or usually after traumas. Lesions occur in backing regions or areas predisposed to trauma and result in scar with or without whiteheads.^{1,5} It can cause serious complications and can be associated with other systemic dis-

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eases.¹ The histologic analysis of the lesion shows subepidermic bulla, with varied dermic inflammatory infiltrate¹ The EBA is characterized with direct immunofluorescence, by the linear deposition of immunoreagents (deposits of IgG and C3) in the dermoepidermic junction.^{1,3} The indirect immunofluorescence of the patient serum can show the antibodies. In the *salt-split skin* technique autoantibodies can be found on the dermic side, after artificial cleavage⁶.

Treatment is frequently disappointing and difficult.^{1,7,8} Recently, new promising therapeutical modalities have been reported such as cyclosporin, colchicine, plasmapheresis, extracorporeal photochemotherapy and above all, intravenous immunoglobulin (IgIV).^{1,7,8}

CASE REPORT

Female patient, aged 54, complained about the appearing of flaccid and tense bullae for six years, some of them hemorrhagic, others with clear content (Picture 1). Clinical examination found not only the mentioned bullae but also erosions on the oral and conjunctival micosas, associated with scars and white-heads, without unguual onset (Pictures 2, 3 and 4).

Histopathologic exam showed subepidermic bulla and lymphocytary infiltrate on the superior dermis; direct immunofluorescence showed linear deposit of IgG, IgA and C3 in the basal membrana zone and indirect immunofluorescence (*salt-split skin*) revealed deposit of IgG in the dermic side of the bulla, confirming the diagnosis of EBA (Picture 5).

The patient was treated with high doses of prednisone (100 mg/day), and thalidomide (100 mg/day). The disease developed new lesions, hoarseness, epistaxis and dysphagia apart from high blood pressure and diabetes as consequences of corticotherapy. Even with



PICTURE 2: Erosive lesion on the oral mucosa

the introduction of methotrexate and dapsona, after four months the patient presented respiratory failure because of laryngeal stenosis being even necessary a tracheostomy (Picture 6). Due to the fact that it was a refractory case, it was decided to treat the patient with intravenous human immunoglobulin 400mg/Kg/day, for five consecutive days (six cycles every four weeks) with important clinical improvement.

DISCUSSION

The EBA, as it was shown in the reported case, is a potentially serious and limiting disease. Its conventional treatment is many times frustating, with modest clinical result, short remissions and many recidiations. The lesions frequently located on the hands and feet limit, a lot, the daily activities of patients.¹

Conventional therapy presents modest clinical



PICTURE 1: Hemorrhagic bulla



PICTURE 3: Erosive lesion on the conjunctiva mucosa



FIGURE 4: Scars and whiteheads



FIGURE 6: Laryngeal stenosis demanding tracheostomy

result and consists of using systemic corticosteroid in high doses, for long periods of time, in monotherapy or in combination with immunosuppressive agents.⁷ The immunosuppressive adjuvants, such as azathioprine, methotrexate, and cyclophosphamide, and the antiinflammatories like dapsone and thalidomide, are used not only because of their corticosteroid saving effect but also to try to induce remission in patients when the disease is refractory to treatment with corticosteroids singly. New therapeutics have been used in a limited number of cases: colchicine, cyclosporin, plasmapheresis, extracorporeal photochemotherapy and IgIV.¹

As the patient did not present a satisfactory response to conventional corticotherapy treatment combined with thalidomide, methotrexate and dapsone apart from the fact that the patient also presented important side effects, IgIV therapy was consid-

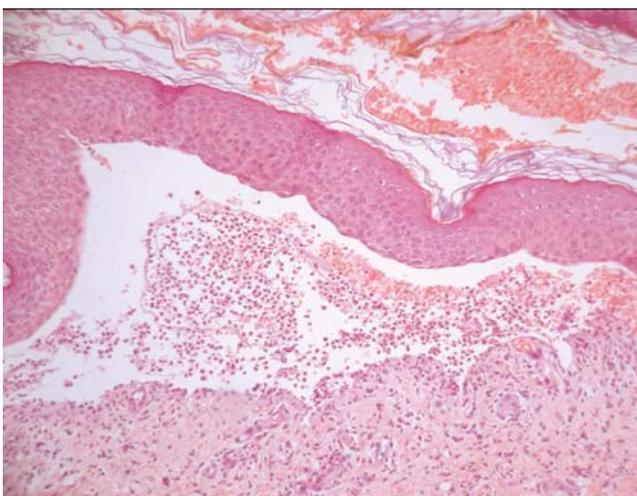


FIGURE 5: Subepidermal bulla with lymphocytic infiltrate on the superior dermis

ered. According to preliminary studies IgIV can bring great benefit for the treatment of EBA.^{1,7,15}

The reagent used in the IgIV therapy is a product prepared from serums obtained from 1000 to 15000 donors per lot.^{1,7,13} Immunoglobulin acts modulating the autoimmune response, occurring reduction on the titer of antibodies, apart from its neutralization.^{12,13}

The most frequent side effects associated with this therapy are fever, chills, rubor, headache, myalgias, nausea and tachycardia. Serious secondary effects such as haemolysis, transitory neutropenia, acute kidney failure, aseptic meningitis and anaphylaxis⁸ may occur. The patient presented minor sialorrhoea.

The recommended dose of IgIV is 400mg/kg/day, for five days, totalizing 2g/kg per cycle, in slow infusion for approximately four hours. It is repeated a new cycle every four to six weeks.^{1,7,8}

After the therapy the patient presented stabilisation of the disease, with decrease in the number of lesions after minor traumas and improvement in the process of healing.

Although the high cost of the treatment is a limiting factor, the IgIV proved to be a viable therapeutic option, efficient and with good tolerance by patients, bringing important improvements on the cutaneous fragility, decrease in lesions and improvement in the quality of life of patients and therefore should be considered, at the beginning of the disease, before the appearance of complications generated by the treatment and by the disease itself. □

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