

# Linear IgA/IgG bullous dermatosis - successful treatment with dapsons and mycophenolate mofetil \*

Dermatose por IgA e IgG linear: relato de caso com boa resposta terapêutica à dapsona e ao micofenolato mofetil

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**Abstract:** A 21-year-old female presenting linear IgA and IgG disease initially responded well to dapsons therapy. However, the treatment with dapsons was withdrawn due to severe anemia induced by malaria, which led to worsening of the clinical picture. Although prednisone and methylprednisolone were tried, the patient responded only to the association of dapsons and mycophenolate mofetil.

**Keywords:** Dapsons; Immunoglobulin A; Immunoglobulin G; Receptors, IgG

**Resumo:** Relata-se o caso de paciente feminina, de 21 anos, com dermatose por IgA e IgG linear. Inicialmente, a resposta clínica foi favorável à dapsona. Após a interrupção desta medicação, por crise de anemia sintomática, precipitada por malária, houve piora da doença, apesar da utilização da prednisona e pulsoterapia com metilprednisolona. A reintrodução da dapsona, associada ao micofenolato mofetil, possibilitou o controle da enfermidade.

**Palavras-chave:** Dapsona; Imunoglobulina A; Imunoglobulina G; Receptores de IgG

## INTRODUCTION

Linear IgA dermatosis (LAD) is defined as an acquired autoimmune bullous disease, characterized by linear deposition of IgA along the basement membrane zone (BMZ).<sup>1,2</sup> Despite the difficulties in distinguishing subepidermal bullous diseases, as of 1979 LAD has been differentiated from herpetiform dermatitis. Since then, bullous diseases with subepidermal cleavage and linear deposition of IgA along the BMZ have been automatically classified as LAD.<sup>3,4</sup> In 1998, Honokik and cols demonstrated the presence of IgG against circulating epidermal antigens in LAD patients.<sup>5</sup> Subsequent reports corroborate the findings of this group.<sup>3,6-8</sup>

The presence of simultaneous linear deposition of IgA and IgG was fundamental for the conception of a new clinical-pathological entity, IgA and IgG linear dermatosis (LAGD).<sup>9,10</sup> However, the magnitude and clinical relevance of this classification remain controversial, as there seems to be no differences in the dermatological presentation and therapeutic spectrum of both diseases. The reason for such similarity has been attributed to the fact that IgA is an antibody with very heterogeneous target antigens, against several BM components. A possible mechanism of intermolecular expansion of epitopes could be responsible for the autoimmunity extension of BP180 antigen to the

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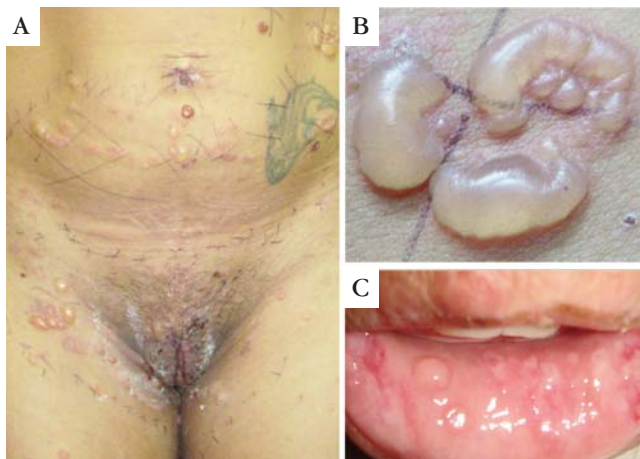
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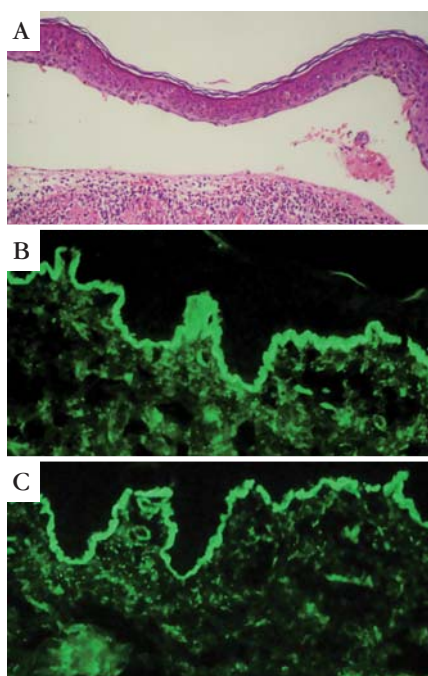
**FIGURE 1:** A. Vesicles and blisters of serous and hemorrhagic content, located on the abdomen and proximal thigh region. The black X marks correspond to a cultural custom, frequent in the Amazon region. B. Closer view of bullous lesions (right thigh). C. Vesicles and exulcerations on the oral mucosa

BP230 antigen.<sup>3,5-8,11</sup> In contrast, IgG seems to have a much more restricted response.<sup>3</sup>

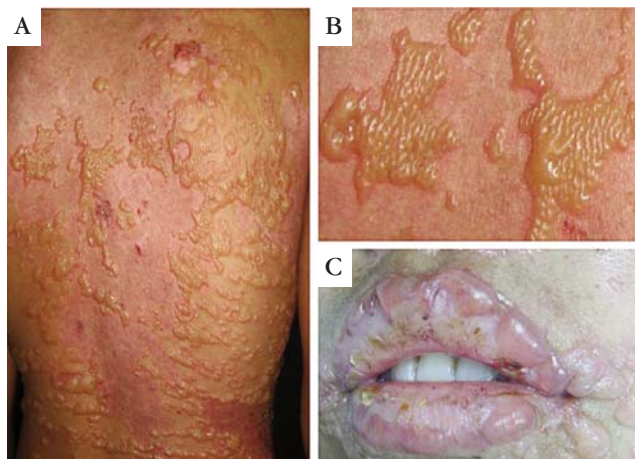
In this study is presented a LAGD case complicated by malaria, but with good response to the treatment with dapsone and mycophenolate mofetil.

**CASE REPORT**

A 21-year old female patient from Manaus (AM) had presented bullous lesions for 21 days, associated with odynophagia and a 10 kg weight loss. She informed that she had suffered from anemia of unknown cause since childhood. Upon physical examination,



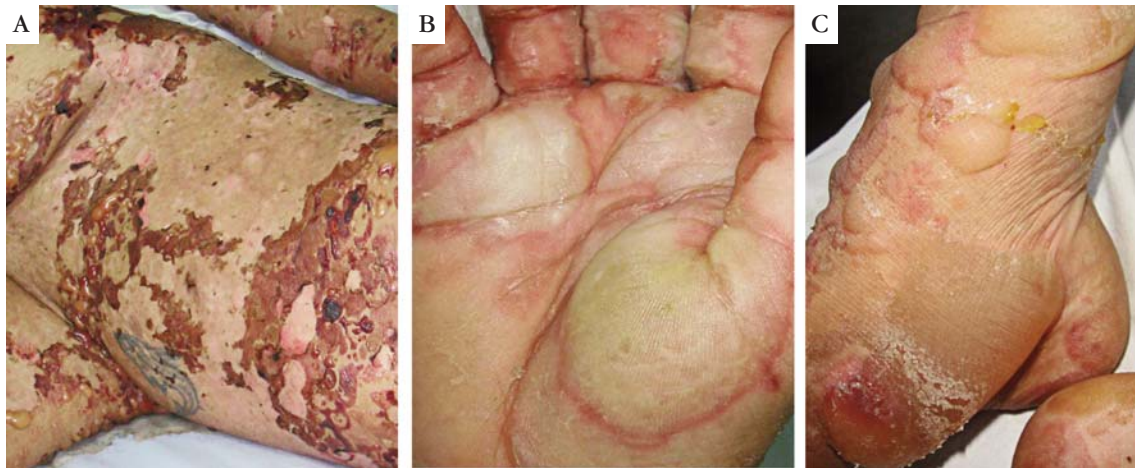
**FIGURE 2:** A. Subepidermal blister with perivascular and interstitial inflammatory infiltrate composed of polymorphonuclear cells (hematoxylin-eosin, 200X). B. Direct immunofluorescence with IgA linear deposition and C - along the basement membrane zone (BMZ)



**FIGURA 3:** A. Vesicles and blisters on the back, two days after suspension of dapsone. B. Closer view of bullous lesions. C. Isolated and coalescent blisters in the lips

vesicles and blisters were observed on an erythematous base and normal skin, located on the abdomen and region close to thighs (Figures 1A and 1B). There were vesicles on the oral mucosa (Figure 1C) and conjunctiva. The glucose, urea, creatinine, cholesterol, triglycerides, ALT, AST, alkaline phosphatase, gamma GT, uric acid, lactic dehydrogenase (LDH) and electrolyte dosages were within normal reference values; urinalysis type 1 was normal. Sputum exam was negative for acid-alcohol resistant bacilli (AARB) and chest X-ray was normal. The hemogram revealed normocytic and normochromic anemia (hemoglobin 9.4g/dL). Histopathological examination found subepidermal blisters and perivascular / interstitial inflammatory infiltrate, composed of few polymorphonuclear cells (Figure 2A). Direct perilesional immunofluorescence revealed linear deposition of IgA, IgG (Figures 2B and 2C) and C3 along the basement membrane zone. The LAGD diagnosis was made based on the histopathological and direct immunofluorescence exams. Dapsone (100 mg/day) administration was started and there was improvement of odynophagia and reduction of skin lesions already in the first week of treatment. Anemia continued to be monitored through regular tests.

Twelve days after the treatment was begun, the patient presented malaria, complicated by symptomatic anemia with blood transfusion indication. During the antimalarial therapy (chloroquine 600mg on the first day, followed by 450mg/day for 2 more days and primaquine 30 mg/day for 7 days), dapsone was maintained. Nevertheless, there was progressive worsening of anemia, with intense asthenia, 14 days after the end of malaria treatment. The increased dosage of LDH and new negative result for *Plasmodium* led to suspi-



**FIGURE 4:** A. Dissemination of cutaneous lesions seven days after interruption of dapsone therapy. B. Bullous lesions on the palm and C. distal third of left leg and foot

tion of hemolysis. Dapsone was suspended and therapy with 60 mg/day of prednisone was begun (1.5 mg/Kg/day). Two days after suspension of dapsone, the patient presented new vesicles and blisters on her back and oral mucosa (Figures 3A, 3B and 3C). Dapsone administration was interrupted and mycophenolate mofetil (MMF) was started, 1g/day. Eight days after the beginning of MMF treatment, there was general worsening of her condition with hypoalbuminemia, anasarca, dissemination of cutaneous lesions (Figure 4A) and the onset of painful blisters on extremities (Figures 4B and 4C). Pulse therapy with methylprednisolone (1g/day) was done for 3 days, with no improvement of the dermatological picture. Despite

the high LDH level (1105U/L), an hemolysis indicator, the other exams excluded the hemolytic anemia diagnosis. Reticulocyte count (1.3%), total bilirubin (0.4g/dL), glucose-6-phosphate dehydrogenase (G6PD) normal activity, serum iron (24mg/dL), transferrin saturation (14%), serum ferritin (856.95ng/mL) and myelogram compatible with erythrocytic hyperplasia defined the diagnosis of anemia by chronic disease, allowing the reintroduction of dapsone at the dose of 100mg/day. Seven days later there was important improvement of the dermatological picture, with involution of bullous lesions after 20 days (Figures 5A and 5B). At present, four months after discharge from the hospital, the patient does not have bullous lesions and continues to take dapsone, 100 mg/day, and MMF, 1 g/day.



**FIGURE 5:** A. Disseminated cutaneous lesions seven days after interruption of dapsone. B. Involution of bullous lesions and complete reepithelization, 20 days after treatment with mycophenolate mofetil and dapsone

## DISCUSSION

The observation regarding treatment of LAGD are the result of studies carried out with LAD patients, since clinical evidence show that when there is linear IgA, independently of the presence of IgG, there is universal therapeutic response to dapsone.<sup>6,12</sup> However, this medication presents important adverse effects; among them, hematological alterations, mainly methemoglobinemia and/or hemolytic anemia. Despite the known predisposition to drug intolerance of patients with G6PD deficiency, even when this enzyme is normal the patient is not exempt from hemolysis risk. The mechanisms through which dapsone produces hemolysis are varied and include formation of haptens, immunocomplexes, free radicals and adsorption of hematic proteins.<sup>13</sup> When there is suspicion of hemolysis, dapsone should be discontinued. In such cases, the main therapeutic alternatives are glucocorticoids, azathioprine, methotrexate, tetracyclines, erythromycin and cyclosporine.<sup>1,6,14</sup> The MMF has been successfully used with LAD patients.<sup>2,15</sup> It is an immunosuppressive agent that inhibits monophosphate

dehydrogenase, the key enzyme in purine synthesis.<sup>2,14</sup> Despite the introduction of MMF in the treatment of the patient, there was worsening of the clinical picture and it was necessary to reintroduce dapsone. This fact could be explained by the long time required for MMF action to begin.<sup>2,15</sup>

An LAGD case of difficult treatment is presented, with the patient presenting malaria and severe anemia. Such intercurrent made the continuity of treatment with dapsone unfeasible. Pulse therapy with oral methylprednisolone and prednisone were ineffective to control the disease. Only reintroduction

of dapsone, in association with MMF, enabled the remission of dermatological manifestations. LAGD is an illness that was only relatively recently recognized, with clinical and therapeutic characteristics that have been linked to studies carried out with LAD patients. The report of cases, mainly those of difficult management like this, is of the essence for future utilization of appropriate therapeutic orientation, based on clinical evidence. □

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