

Diffuse cutaneous bullous mastocytosis with IgM deposits at dermo-epidermal junction

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Abstract: Cutaneous mastocytosis is a disease characterized by the infiltration and proliferation of mast cells in the skin. In children, the most common form of presentation is urticaria pigmentosa, while the diffuse cutaneous bullous mastocytosis is one of the rarest subtypes seen.

The aim of this paper is to present a case of diffuse bullous mastocytosis with detection of IgM deposits at dermo-epidermal junction using direct immunofluorescence microscopy. The diagnosis of diffuse bullous mastocytosis is a challenge, and direct immunofluorescence microscopy is necessary in order to exclude an autoimmune bullous disorder. However, IgM deposits at dermo-epidermal junction can be nonspecific, being found in a variety of skin disorders.

A 6 month-old girl presented with bullous lesions and erosions on the scalp and the trunk. During hospitalization, further bullous lesions appeared, along with generalised erythrodermia. Skin biopsy revealed aspects of urticaria pigmentosa. Taking into account the clinical findings, the case was enclosed as bullous mastocytosis. Treatment included the avoidance of trigger factors, and administration of antihistamines along with a short-term course of systemic steroids. The evolution was favorable, with remission of the existing lesions and without occurrence of new ones.

Introduction:

Mastocytosis is a rare, heterogeneous group of haematopoietic disorders, characterized by an abnormal increase and accumulation of mast cells in one or more organ systems¹. Cutaneous mastocytosis is the most common subtype of mastocytosis, showing mast cells infiltration confined to the skin.

Cutaneous mastocytosis affects predominantly children, early in life, and is known to be a benign condition with resolution by puberty. 55% of cases occur between birth and the age of 2, 10% of cases occur in children between 2 and 15 years old, and 35% of the cases occur after the age of 15².

Although regression of mastocytosis was observed in two-thirds of children, the remaining third continue to present with progressive or stabilized forms of the disease. Therefore, long-term follow-up of children is necessary³.

There are 3 subtypes of cutaneous mastocytosis mentioned in the World Health Organization (WHO) classification, namely 1) urticaria pigmentosa, 2) diffuse cutaneous mastocytosis, and 3) mastocytoma¹. In a recent study performed on 1747 cases, urticaria pigmentosa was found in 74.8%, mastocytoma in 19.5%, and diffuse cutaneous mastocytosis in 5.2% of cases³.

The most common form, as mentioned, is urticaria pigmentosa and this condition is characterized by oval or round-shaped macules, papules or plaques, in various numbers, with typical sparing of the palms, soles, face and scalp⁴.

The diffuse variant is the rarest and the most severe form of cutaneous mastocytosis, which presents with erythroderma, hemorrhagic blisters and in some cases extensive bullous lesions (known as diffuse bullous mastocytosis)⁵. The onset is commonly seen in the first 2 years of life, most frequently triggered by sudden changes in temperature, irritability, fever and teething. Systemic symptoms include itching, flushing, diarrhea, vomiting, hypotension and even anaphylactic shock.

The neonatal onset of diffuse cutaneous mastocytosis is very rare. Until now, only 22 cases were reported in the literature⁶.

Heide et al described two clinical variants of diffuse mastocytosis. The first variant is the “initial bullous presentation” that presents as diffuse erythema, with generalized blistering, which appear early in life. The second variant is the “infiltrative small vesicular type”, which presents with limited vesicular blistering and starts with slowly progressive, diffusely distributed yellow-orange infiltrates that evolve into nodular lesions⁷.

Herein, we present a case of diffuse bullous mastocytosis, showing, as particular findings in direct immunofluorescence (DIF) microscopy, granular IgM deposits at the dermo-epidermal junction.

Although positive DIF is considered specific for the diagnosis of autoimmune bullous diseases, atypical results have been reported in other cutaneous diseases (infections, inflammatory skin disease, genodermatoses, and others)⁸.

IgM deposits at the dermo-epidermal junction can be considered a potential diagnostic pitfall, therefore their possible presence in the case of diffuse bullous mastocytosis must be accounted for.

Report of a patient:

A 6 month-old female infant presented with bullous lesions and erosions on the scalp and trunk. (Figure 1 A; B.). No relevant personal or family history regarding the symptoms was noted. The onset of the disease was insidious, without improvement under local treatment with antiseptic agents. Initially, the case was diagnosed as extensive bullous impetigo and therapy with intravenous antibiotics (Cefuroxim 100mg/kg/day) was started.

The blood count, blood chemistry, and liver function tests were normal. A culture of the liquid from the vesicles was analyzed, showing the presence of *Staphylococcus hominis* and *Enterococcus faecalis*. Both showed sensitivity to Vancomycin. Even if a possible contamination of the culture was taken into account because of the progression of the bullae, antibiotics (Vancomycin 45 mg/kg/day) were administered further without any clinical improvement. On the seventh day of hospitalization the infant presented generalized erythrodermia with the appearance of a new bullous lesion on the back and a positive Darier sign.

After the diagnosis of staphylococcal scalded skin syndrome, congenital syphilis, IgE-mediated allergy, incontinentia pigmenti and epidermolysis bullosa were ruled out, we raised the hypothesis of cutaneous bullous mastocytosis or an autoimmune bullous disease.

A biopsy from lesional and perilesional skin was performed. The biopsy of lesional skin was analysed by classical haematoxylin-eosin (Figure 2 A) and toluidine blue stainings (Figure 2 B). The findings consisted of aggregates of mast cells filling the papillary dermis, and extending into the reticular dermis. The conclusion of the histopathological examination was that the aspect belonged to urticaria pigmentosa, but taking into account the clinical findings, the disorder was enclosed as a diffuse bullous mastocytosis. When the biopsy was analyzed by immunohistochemistry using the CD 117 (c-kit) antibody, mast cells showed a strongly positive staining (Figure 2 C).

DIF microscopy was performed on perilesional skin in order to exclude an autoimmune bullous disease. DIF microscopy showed granular deposits of IgM and at dermo-epidermal junction (IgG, IgA and C3 were negative on DIF) (Figure 2 D).

Abdominal ultrasonography was performed to rule out the involvement of other organs. The serum tryptase level was 15,7 ng/mL (reference values <11,4 ng/mL; suspicion of systemic mastocytosis >20 ng/mL). Because our patient didn't show any manifestations consistent with systemic mastocytosis on physical or laboratory examination, we didn't perform a bone marrow examination.

Intravenous steroids (Methylprednisolone 0.5 mg/kg/day, for 5 days) and antihistamines (Cetirizine 2.5 mg, administered twice daily) were started, leading to a significant regression of erythoderma and the blisters. The patient was discharged with the recommendation of avoiding trigger factors and prescription of antihistamines. Treatment with cetirizine was continued for 1 year.

Shortly after the patient received treatment, all bullous lesions healed with scarring, hypo and hyperpigmentation. One year after the patient was discharged from the hospital, she showed no signs of relapse.

Discussion:

Mastocytosis is a disorder characterized by the accumulation of mast cells in the skin and other organs (bone marrow, liver, spleen, lymph nodes, gastrointestinal tract). According to the type of organ involved, the condition is classified as cutaneous or systemic. Both forms occur in adults as well as in children, with a predominance of the cutaneous form in the pediatric population. Most of the cases present as urticaria pigmentosa (47-75%) and mastocytoma (17-51%), whereas diffuse mastocytosis represented only 1-8% of the cases⁹.

There is no well established diagnosis checklist for systemic mastocytosis in children. In adults the diagnosis is based on the following criteria:

1. Major criterion: multifocal compact mast cells infiltrate (with mast cells aggregates of 15 or more cells) in histological sections.
2. Minor criteria
 - a) Detection of an activating point mutation at codon 816 of KIT in bone marrow, blood or other extracutaneous organs;
 - b) Mast cells in bone marrow, blood or other extracutaneous organs express CD2 or/and CD25 in addition to normal mast cell markers;
 - c) Serum tryptase levels permanently over 20 ng/ml (with the exception of associated clonal myeloid disorder);
 - d) In biopsy sections of bone marrow or other extracutaneous organs, more than 25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology or, of all mast cells in bone marrow aspirate smears, more than 25% are immature or atypical.

The diagnosis of systemic mastocytosis can be made when the major criterion and one minor criterion, or at least three minor criteria are fulfilled¹⁰.

One study performed by Lange et al in 2014 showed that the mast cells from the skin displayed immunoreactivity for CD2 or CD25 in 57,1% of cutaneous mastocytosis and in 90,3% of systemic mastocytosis. Also, the presence of CD2 or CD25 was detected in 84,2% of patients with the KITD816V mutation in the bone marrow. The authors also showed a positive correlation between the density of CD117 and CD25 positive mast cells in the skin infiltrates of systemic mastocytosis patients and the lack of a similar correlation in the skin of cutaneous mastocytosis patients. However, their conclusion is that the bone marrow mast cells

immunophenotype is more specific for systemic mastocytosis than CD2 and/or CD25 expression on skin mast cells¹¹.

In our case, a systemic involvement was ruled out by clinical examination and ultrasound, the absence of abnormalities on peripheral blood counts, low level of serum tryptase, and the resolution of symptoms with treatment.

The differential diagnosis, clinically, included infections (viral infections, bacterial infections, or mycotic infections), genetic diseases (epidermolysis bullosa, epidermolytic hyperkeratosis, incontinentia pigmenti), autoimmune bullous diseases, most of the authors confirming that the diagnosis of bullous mastocytosis is a difficult one¹²⁻¹⁴. This happened in our case as well, the condition being at first mistaken as bullous impetigo. Furthermore, congenital syphilis was suspected, but the serology was negative. IgE-mediated allergy was ruled out as well, total IgE being within the normal ranges of the age group.

The diagnosis of cutaneous mastocytosis is based on clinical aspects, skin biopsy and the absence of criteria for systemic mastocytosis. Usually, DIF microscopy is performed for the diagnosis of autoimmune blistering skin diseases. In the majority of cases, positive staining on basement membrane indicates a subepidermal autoimmune bullous disease.

The diagnostic criteria for autoimmune bullous diseases cover the clinical picture, which usually comprises blistering of skin and mucous membranes (erosions, crusts, erythema), and the histopathology investigation, which shows a subepidermal cleavage or an intraepidermal cleavage. The next step for the diagnosis of subepidermal bullous diseases is the DIF microscopy that indicates linear IgG/IgA/C3 or granular IgA at the basement membrane. Indirect IF microscopy on salt-split-skin shows binding at the epidermal side or at the dermal side. More specific investigations, such as ELISA or immunoblot, are required in order to detect the specific protein involved: BP 180, BP 230, collagen VII, laminin γ 1, laminin 332, or epidermal/tissue transglutaminase¹⁵.

The pathogenesis of bulla formation in diffuse mastocytosis is unknown. In one study performed on IgA bullous dermatosis, the authors showed that activated mast cells (tryptase-positive) produce IL-8, which is a potent proinflammatory cytokine. In addition, activated keratinocytes, which express an intense intracytoplasmic and membrane staining for IL-8, participate in the inflammatory process that induces formation of the bullous lesion¹⁶.

Other studies showed that the degranulation of mast cells could be a result of complement activation and formation of C3a and C5a anaphylatoxins¹⁷, but also neuropeptides and cytokines that are involved in mast cells' degranulation¹⁸. Granules and protease-heparin proteoglycan complexes are released from mast cells and produce cleavage of the basal membrane components directly¹⁹ or by activation of collagenolytic metalloproteinases²⁰. The authors showed that mast cell tryptase, alone or in combination with metalloproteinases, can participate in the destruction of the basal membrane, the target being the fibronectin²¹.

Mast cells express KIT, a transmembrane tyrosine kinase receptor for stem cell factor. The interaction between KIT and stem cell factor plays an essential role in the development of

mastocytosis²². Pediatric mastocytosis is considered a clonal disease, and 40% of KIT mutations in children occur in exons 8-11³.

The presence of IgM in bullous mastocytosis is a particular finding for the described case. We wanted to draw attention to the fact that the diagnosis of diffuse cutaneous mastocytosis, especially in terms of contrasting it with the autoimmune diseases, can be complicated by the immunofluorescence findings.

The most likely cause for the IgM deposits is the pronounced cutaneous inflammation, and does not indicate an autoimmune process.

To our knowledge, there is no previous report in the medical literature of positive DIF findings in a patient with diffuse mastocytosis. Different patterns of IgM staining have been described in the medical literature: linear, granular, linear granular, diffuse linear and band-like granular. The granular pattern is found more frequently in lupus erythematosus but is also encountered in other conditions²³⁻⁴⁵ (Table 1).

The pathogenic role of autoantibodies from patients with autoimmune blistering diseases to dermo-epidermal junction proteins in blister formation is supported by clinical observations and experimental evidence⁴⁶.

Deposition of immunoreactants at the basement membrane is a characteristic feature in lupus erythematosus, but the mechanism is not clear. These immunoglobulins could be circulating immune complexes of DNA and antinuclear antibodies trapped within the dermo-epidermal junction⁴⁷. However, there has been reported a great number of other conditions, including cutaneous infections, inflammatory skin diseases, vesicular eruptions, that yield positive DIF findings without an exact mechanism⁸.

To date, there is no cure for mastocytosis. Of utmost importance is the avoidance of trigger factors such as those mentioned above, but also of the histamin-liberator drugs and food. The treatment relies on antihistamines and mast-cell stabilizers⁴⁸. Steroids are used topically or systemically, in case of more severe skin lesions. PUVA therapy is reserved for unresponsive cases in adults, because of the risk of side effects.

Our patient received antihistamines and systemic steroids, with a good improvement of the skin lesions and erosions. Food and skin cosmetics were switched to hypoallergenic formulas. Observation of the patient with regular follow-up was considered the best option in this case.

Literature mentions a favorable prognosis of cutaneous mastocytosis in children, with a complete resolution by puberty^{49,50}. Ben-Amitai et al.⁵¹ lists in his study a total resolution or marked improvement in 92,5% of the patients, while Kiszewski et al.⁵² reports a proportion of 80%, which indicates a great chance of improvement in childhood cutaneous mastocytosis. Because of the lack of reliable prognostic clues for predicting the risk of systemic involvement, follow-up and regular investigations are indicated.

In conclusion, the diagnosis of diffuse cutaneous mastocytosis is difficult and is based on clinical appearance and laboratory explorations, including blood tests, histopathology, and immunohistochemistry. DIF microscopy is required to exclude autoimmune bullous diseases

but physicians should be aware of the fact that this examination may show positivity in a large number of cutaneous disorders.

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Figure 1 A) Blisters and erosions on the scalp; B) Erosion after the breaking of a blister.

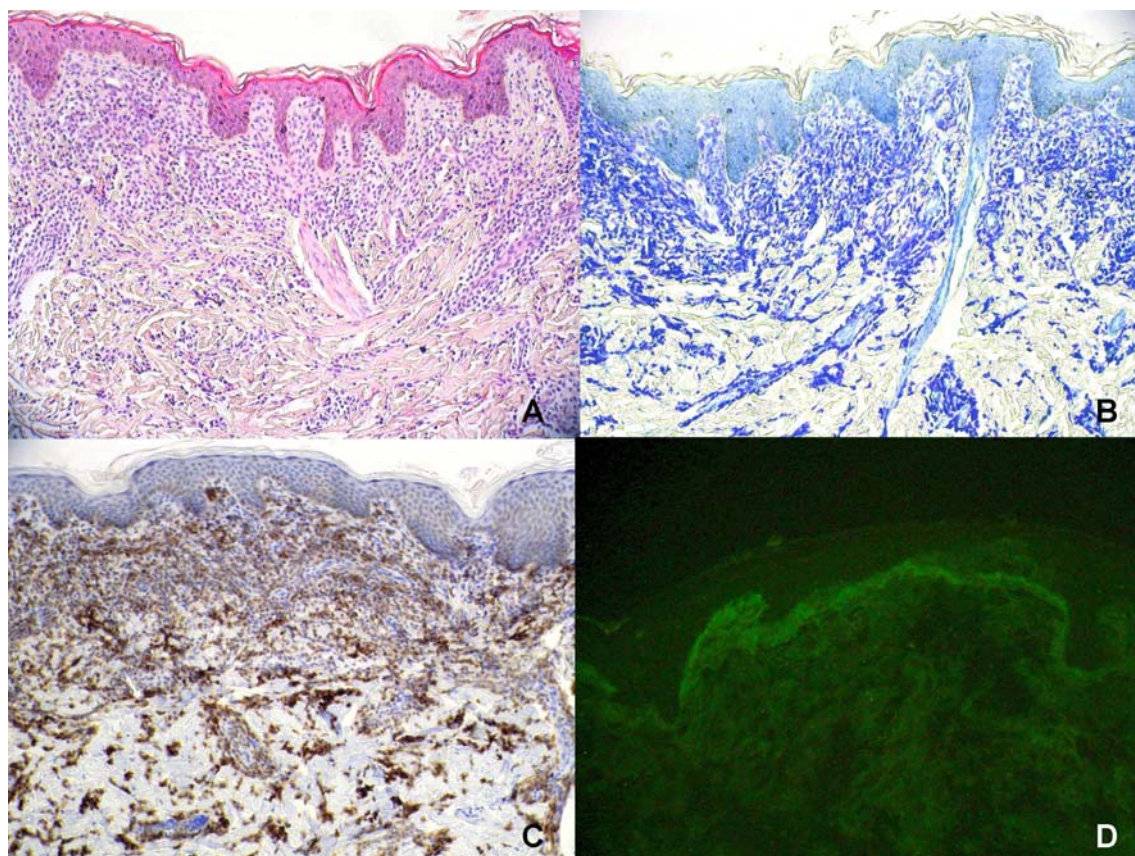


Figure 2 A) The presence of mast cells in the dermis (hematoxylin/eosin, x10); B) Mast cell infiltration in the upper dermis, positive toluidine blue staining (x10); C) mast cells strongly expressing CD 117 (c-kit) antigen; D) Direct immunofluorescence shows granular band of IgM at the dermoepidermal junction.