

# Single Case Report: Diffuse Cutaneous Mastocytosis with Generalized Bullae Mimicking Bullous Pemphigoid

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**Keywords:** Diffuse cutaneous mastocytosis, mastocytosis bullous, bullous pemphigoid

**Abstract:** Introduction: Mastocytosis is a rare disease; it is defined as mast cell infiltration in some organs. Skin is the most commonly involved organ. Diffuse cutaneous mastocytosis is a form of skin mastocytosis which can be manifested as bullous lesions. Case: A 3-month-old male infant is presented with generalized dermatosis, characterized by multiple blisters and brownish spots all over his body since one month ago. On dermatologic examination, multiple tense bullae of various sizes with brown macules and plaques are located throughout the body. Some bullae rupture to form an erosion. Darier sign shows erythema/mild urticaria lesions (positive). Routine blood tests within normal limits. The histopathologic examination reveals sub-epidermal bullae with an inflammatory cell and the dermis is filled with inflammatory cells and mast cells. Patients were diagnosed with diffuse cutaneous bullous mastocytosis. The patient was treated with 0.9% NaCl compresses, 2% mupirocin cream, and 0.1% betamethasone cream. Monitoring therapy is done routinely to evaluate the prognosis of the disease. Discussion: Diffuse cutaneous bullous mastocytosis is one of the rarest forms of skin mastocytosis. Cutaneous mastocytosis in children who persist until adolescence develops systemic mastocytosis in 15-30% cases so early diagnosis of mastocytosis in children is very important to get a good prognosis. Conclusion: Diagnosis of diffuse cutaneous mastocytosis is not easy because the prevalence is difficult to determine and often misdiagnosed. Here, we report this case due to the similarity of clinical manifestation of bullous diseases, especially in a newborn with scattered blisters and erosions.

## 1 INTRODUCTION

Mastocytosis is a disease which shows a large number of abnormal proliferation and accumulation of mast cells in one or more organ systems including the skin, bone marrow, liver, spleen, lymph nodes and digestive tract with various variants of clinical manifestations (Dines et al, 2014). There are two types of mastocytosis that are cutaneous mastocytosis (CM) and systemic mastocytosis (SM). CM is often found in children, whereas SM is more common in adults (Lange et al, 2015). According to the 2017 World Health Organization (WHO) classification, CM encompasses urticaria pigmentosa or maculopapular cutaneous mastocytosis (UP), diffuse cutaneous mastocytosis (DCM), and mastocytoma in the skin. The bullous eruption is most commonly associated with DCM, although bullae can occur in all forms of cutaneous mastocytosis (Hans et al, 2018). In patients with

DCM, bullous eruptions are widespread during the early stages of life. The blisters present in a variety of sizes and initially contain clear fluid that may become hemorrhagic with time and can leave a hyperpigmented brown macula. Bullous lesions may occur in linear or grouped fashion and often develop on the trunk, scalp, and extremities. The bullous lesions typically resolve by 3-5 years of age. A small number of patients have been reported with yellow-orange infiltrated. Over time, the skin becomes thickened and has a doughy consistency. Other cutaneous manifestations may include pruritus, urticaria, a positive Darier's sign and marked dermatographism (Metcalfe et al, 2016; Eui et al, 2010).

The prevalence of mastocytosis is still challenging to determine, but it is estimated that the incidence of mastocytosis is around 5-10 per 1,000,000 inhabitants per year. This disease can occur at any age. Approximately 50% of the onset of

mastocytosis that occurs in children can appear during infancy, especially in the neonatal period until the age of 2 years. There is no racial difference and sexual dominance in this disease (Metcalf et al, 2016).

Spontaneous resolution of 50-60% of bullous lesions can occur in most patients with DCM until before the age of 5 years. However, reliable prognostic clues are lacking, especially for predicting the risk of systemic involvement with life-threatening manifestations that they should undergo annual investigations and careful follow-up (Lange et al, 2015; Magliacanel et al, 2014).

## 2 CASE

A 3-month-old male infant is checked in a polyclinic with generalized dermatosis characterized by multiple blisters and brownish spots all over his body since one month ago. According to his mother, since the age of 1 month, the blisters appear for the first time in the abdominal area. One month later, blisters spread over the limbs, trunk, and scalp. When the blister bursts, it will leave behind red which then becomes brownish spots. History of flushing, complaints of vomiting, and diarrhea in patients are denied. Due to the distance of health facilities are far from where they live, patients have never been taken to a health facility and have never received treatment. The patient was the third child with a history of normal birth, spontaneous crying with a birth weight of 2900 grams. There is no history of the same complaints in previous births. There is no history of asthma and allergies in the patient's family.

Physical examination within normal limits, and there are no abnormalities or congenital disabilities experienced by the patient. Dermatologic examination revealed skin was dry and facial skin is thickened with numerous tense bullous vary in size over normal skin et regio temporooipital, oralis, mentalis, medial antebrachii sinistra, and femoralis dextra posterior. Multiple erosions vary in size are seen on regio infraclavicularis, lateral dextra brachii posterior and vertebralis. Brownish plaques and macules vary in size circumscribed multiple discrete et regio abdominals, antebrachii dextra et sinistra, vertebralis and anterior-posterior femoralis dextra et sinistra (Figure 1). Darier sign shows erythema lesions (positive). Examination of the Nikolsky sign is negative. Based on the anamnesis and physical examination, we considered diffuse cutaneous mastocytosis bullous, bullous

pemphigoid, and bullous epidermolysis as a differential diagnosis. Routine blood tests within normal limits. Patients were then biopsied on bullae lesions which are newly formed less than 24 hours located in the medial region of the left antebrachii. Histopathologic examination results with staining of hematoxylin-eosin, showing sub-epidermal blister with a dome consist of squamous epithelial cells, an inflammatory cell eosinophils in bullae. Mast cells densely filling the dermis below the blister accompanied by vascular congestion and dilatation (Figure 2). Examination of spinal cord aspiration was not carried out in these patients because they did not get the consent of the patient's parents. To assess the extent and activity of skin lesions, the SCORMA Index was applied with result 51.8.

The diagnosis of DCM was made based on these clinical and histopathological findings. Patients were given 0.9% NaCl compress therapy in erosion lesions for 15-20 minutes every 6 hours a day, 2% mupirocin cream and 0.1% betamethasone cream every 12 hours a day.

## 3 DISCUSSION

The diagnosis of CM, in this case, is based on history, clinical manifestations, histopathologically examination, and the absence of signs of systemic mastocytosis. Organomegaly examination (hepatomegaly, splenomegaly, lymphadenopathy) is needed to look for systemic involvement. A peripheral blood examination is needed to look for hematologic abnormalities related to bone marrow involvement. (Lange et al., 2015; Eui et al., 2010) The most common variant of CM is UP, that it manifests as 0,5- 1 cm yellowish-tan to red-brown macules or slightly raised papules. The affected areas include the trunk and extremities, while the face, scalp, palms, and soles tend to be free of lesions. DCM is an unusual variant of the mast cell disease characterized by widespread bullae as its main cutaneous feature. DCM can appear at birth (congenital and neonatal) or in early infancy. Widespread involvement of the skin with blistering and bullae may be the presenting symptoms. The skin may be leathery and thickened ("peaud' orange") due to infiltration with mast cells. Hyperpigmentation may persist into adulthood, and dermographism may be prominent. 6,7 We diagnosed our case as DCM since there were multiple bullae all over his body including face, scalp, trunk and limb as its main cutaneous feature and without systemic involvement.

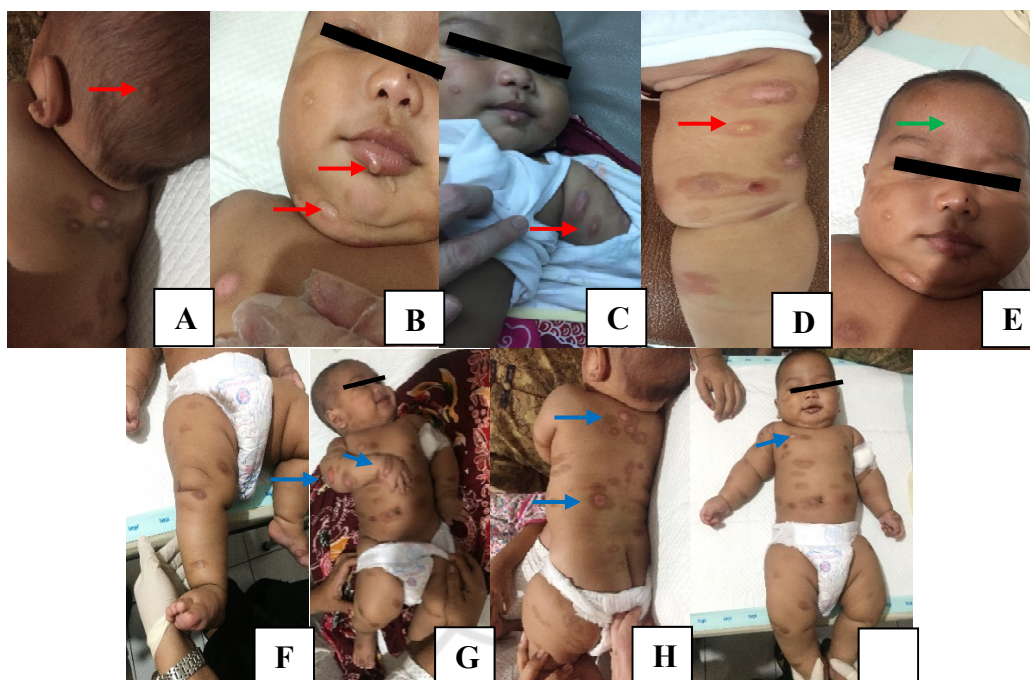


Figure 1. Three-month-old infant with numerous tense bullous vary in size over normal skin et regio temporooecipital, oralis, mentalis, medial antebrachii sinistra and femoralis dextra posterior (red arrow)(A),(B),(C),(D) and the facial skin is thickened especially forehead (green arrow) (E). Multiple erosions vary in size are seen on regio infraclavicularis, lateral dextra brachii posterior and vertebralis (blue arrow) (G),(H) and (I). Brownish plaques and macules vary in size circumscribed multiple discrete et regio abdominal, antebrachii dextra et sinistra, vertebralis and anterior posterior femoralis dextra et sinistra.

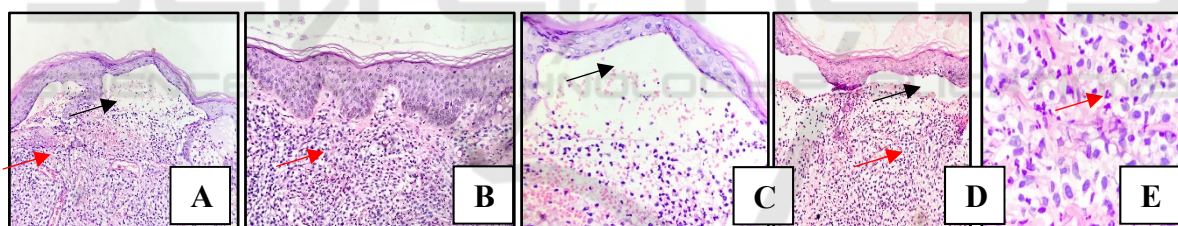


Figure 2. Sub-epidermal blister with a dome consists of squamous epithelial cells, an inflammatory cell eosinophils in bullae (black arrows) (A), (C) and (D). Mast cells densely filling the dermis below the blister accompanied by vascular congestion and dilatation (red arrows) (A), (B), (D), and (E).

The clinical manifestations of various bullous diseases in children are almost the same, so clinical diagnosis is not enough. To confirm mastocytosis in bone marrow or in blood, the mast cell count should be more than 20% of the nucleated cells in the bone marrow or >10% peripheral blood leukocytes. However, systemic investigations such as bone marrow aspiration/biopsy or serum total tryptase level could not be performed because of the reluctance of the parents. Histopathological and immunofluorescence exams, particularly DIF (direct immunofluorescence) are needed for diagnosis. (Heide et al., 2009). According to WHO (2017), the terminology of mastocytosis on the skin can be

established from the results of histopathological biopsy exams that prove the infiltration of mast cells in the dermis, and there is no involvement of other organs or signs of SM. Usually, because no bone marrow examination was performed and/or clinical information is lacking. Tran et al. reported that in the case of CM there was a large amount of infiltration of eosinophil cells originating from chemotactic eosinophils a factor secreted by neoplastic mast cells in the dermis. (Hans-Peter et al., 2018; Arber et al., 2016)

There are two important biological findings as markers related to the pathogenesis of mastocytosis disease; the presence of somatic

mutations in KIT genes (usually KIT Asp816Val D816V mutations) and the presence of immunophenotype deviations associated with CD25 and c-KIT gene expression CD117 which plays a role in differentiation, maturation, and proliferation of mast cells. (Arock et al., 2015; Walker et al., 2006) Mutations from oncogenic KIT D816V are usually detected in almost 80% of patients with SM. Mutations KIT D816V is rarely found in CM patients. As a result of mutations in the c-KIT gene, this will result in an increase in abnormal proliferative activity of mast cells. Mast cell degranulation causes the release of various mediators such as histamine, the slow-releasing substance of anaphylaxis (SRSA), eosinophil chemotactic activating factor (ECAF), heparin and other mediators that play a role in the Darier sign mechanism. Darier's sign, which is defined by wheeling and reddening of lesions upon mechanical stroking or rubbing, is usually demonstrable. It is not always positive in adult patients but usually positive in pediatric patients. The Darier's sign is often not elicited correctly, resulting in false-negative or false-positive results. (Tran et al., 2014)

In bullous pemphigoid, IgG autoantibodies are attached to BP180 antigen (transmembrane glycoprotein hemidesmosome). The IgG bond and BP180 antigen will activate complement. The complement will cause degranulation of mast cells and withdrawal of neutrophils and eosinophils, which will release various inflammatory mediators and proteinases that cause subepidermal domes. However, there is no histopathological infiltration of mast cells in the dermis in the bullous pemphigoid, and the Darier sign does not show erythema/urticaria lesions (negative). (Wada et al., 2016)

Because there is still no curative treatment for mastocytosis, the available therapeutic options are mostly palliative and symptomatic. In the treatment of CM that occurs in children, it is recommended to give topical medium-class steroids immediately. Topical steroid applications in CM that occur in children have been shown to eliminate local skin symptoms, and Darier's sign becomes very weak until it disappears. Treatment with topical steroids is still better and effective in the case of cutaneous mastocytosis considering the long time required for the spontaneous disappearance. (Annalisa et al., 2015) Hartmann et al. in a randomized study of multiple parallel and case-control trials, it was explained that the topical use of clobetasol for two weeks in 39 patients with CM had a significant effect on reducing the size of lesions and the number of mast cells in the upper dermis. (Hartman et al.,

2010) In our case patient giving 0.1% betamethasone cream and 2% mupirocin cream every 12 hours a day to prevent secondary infections in open wounds. In the treatment of mastocytosis in addition to medical treatment, it is essential to maintain nutrient intake, which can trigger the release of mast cell mediators. We can see some food ingredients that must be watched out for sufferers of mastocytosis such as; Monosodium Glutamate (MSG), alcohol, shellfish, artificial food dyes and flavorings, food preservatives, pineapples, tomatoes & tomato-based products, and chocolate. (Annalisa et al., 2015; Hartman et al., 2010). In our case, we educate the patient's mother so that after entering the complementary stage of breastfeeding, it can be more attentive and careful about food ingredients that can trigger the release of histamine mediators.

There are still many controversies in defining and evaluating mastocytosis. One of the aspects that are missing is a system for clinical evaluation of mastocytosis of the skin. The clinical use of the scoring index of mastocytosis (SCORMA). The scoring of the SCORMA Index was designed in order to assess the extent and activity of skin lesions. It is based on a semi-quantitative analysis of the extent, intensity, and subjective complaints, and it ranges from 5.2 to 100. (M. Lange et al., 2012)

Despite progress in understanding the pathogenesis, genetics, and diagnostic criteria of mastocytosis, reliable prognostic clues are lacking, especially for predicting the risk of systemic involvement. According to some, most DCM cases about 50% of patients tend to improve with time, whereas others concluded that DCM patients are at higher risk of developing SM or life-threatening events such as hypotension or bronchospasm. Cutaneous mastocytosis in children who persist until adolescence develops SM in 15-30% cases. Therefore, evaluation of the prognosis assessment of cutaneous mastocytosis in children is essential to determine whether or not an attempt is made to seek systemic involvement. (Hartman et al., 2010; M. Lange et al., 2012).

#### 4 CONCLUSION

Due to the similarity between bullous pemphigoid and CM, we must be considered in the differential diagnoses of bullous eruptions, especially in a newborn with scattered blisters and erosions. It could be concluded that pediatricians and dermatologists should remain aware of varied forms of cutaneous mastocytosis because of its rarity

and the distinctive management of each individual case. Our case helps to document the diagnosis of CM in the pediatric patient population.

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