Bullous Urticaria Pigmentosa in an Infant: A Rare Form of Bullous Disorder

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Abstract: Mastocytosis is a rare, sporadic, and a heterogeneous group of hematopoietic disorder, characterized by an enormous number and accumulation of mast cells in one or more organ systems. The prevalence of mastocytosis is challenging to determine due to underdiagnosis. Pediatric-onset mastocytosis which was commonly diagnosed before two years of age is generally a benign disease. The course of pediatric-onset mastocytosis is variable, from birth to the first year of life, with an average of 2.5 months. Cutaneous mastocytosis may manifest as urticaria pigmentosa, diffuse cutaneous mastocytosis, and telangiectasia macularis eruptive perstans. Bullous urticaria pigmentosa is a rare variant of urticaria pigmentosa. Blistering is considered to be an effect of free mediator activity. The symptoms are mostly in proportion to the mast cell degranulating activities in tissues, which may appear in the first year of life. Although systemic involvement is rare in pediatric cutaneous mastocytosis, blistering may promote secondary infection and electrolyte imbalance. We report a four-month-old infant with bullous urticaria pigmentosa. The symptoms had appeared since the second day of life. Routine hematology examination revealed mild microcytic hypochromic anemia. Skin biopsy from the lesional skin revealed diffuse dermal infiltration of mast cells, some showing granules and scanty cytoplasm which supported the diagnosis of urticaria pigmentosa. The patient was managed with antihistamines. In two-month-period of follow up, the development of new lesions is slowing.

1 INTRODUCTION

A mastocytosis is a heterogeneous group of myeloid neoplasms with abnormal proliferation and accumulation of mast cell in one or more organ systems. (Asati DP et al., 2014) During 2015-2019, there are 12 new cases of cutaneous mastocytosis in Pediatric Dermatology Division, Department of Dermatology and Venereology Faculty of Medicine Universitas Indonesia/ Dr. Cipto Mangunkusumo National General Hospital. (Data Kunjungan Poiklinik Dermatologi Pediatri Departemen Ilmu kesehatan Kulit dan Kelamin FKUI/RSCM, 2015-2019). (Asati DP et al., 2014;Barros et al., 2014) reported two cases of congenital urticaria pigmentosa in twin babies. (Barros et al., 2014) Year 2005 Working Conference on Mastocytosis' classified mastocytosis into three major categories: cutaneous mastocytosis, systemic mastocytosis and extracutaneous mast cell proliferation. (Van Gysel D et al., 2011) The cutaneous form consists of urticaria pigmentosa, mastocytoma, diffuse cutaneous mastocytosis, and telangiectasia macularis eruptive perstans in their order of their frequency. (Asati DP et al., 2014)The diagnosis of cutaneous mastocytosis (CM) is based on clinical and histological findings in the skin, together with the absence of criteria that would allow the diagnosis of systemic mastocytosis. In cutaneous mastocytosis, the visible cutaneous abnormalities are most often of major concern to the patient and their family. (Van Gysel D et al., 2011)
Urticaria pigmentosa is by far the most common variant (70-90%) of childhood mastocytosis. The lesions commonly appear in the first year of life and maybe present at birth. The eruption consists of slightly elevated, skin-colored, brown-red or yellow macules, plaques or nodules. (Van Gysel D et al., 2011) Urticaria pigmentosa presenting with a vesicular and bullous lesion as the predominant feature is a rare entity. (Chintagunta SR et al.,2017).

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The lesions occur in a generalized distribution but tend to be of highest density on the trunk. (Van Gysel D et al., 2011).Less affected are palms, soles, scalp, and face, as well as sun-exposed body areas. (Chintagunta SR et al.,2017).

In the first two years, Urtica and erythema may occur spontaneously or after stroking a lesion (Darier's sign), although Darier's sign is not always present in all patients. (Van Gysel D et al., 2011;Castells M et al., 2011)

All pediatric cutaneous forms of mastocytosis can rarely present with acute mast cell degranulating events, such as anaphylaxis, whole body flushing, dyspnea, wheezing, vomiting, diarrhea and sometimes cyanotic spells (Castells M et al., 2011;Tharp MD et al., 2012)

The diagnosis of cutaneous mastocytosis requires a history of new-onset skin lesions with or without systemic symptoms. A physical examination with a positive Darier's sign, supported with increasing serum tryptase and dermal infiltration of mast cell on skin biopsy is essential for building the diagnosis. Analysis of c-kit mutations is recommended. In addition to the skin biopsy, bone marrow studies are recommended if the tryptase is significantly elevated, severe systemic symptoms are present, if there is associated organomegaly or if there is no significant response to initial symptomatic therapy. Parents should be explained carefully about the possibility of evolution to a systemic form in a small number of cases.(Castells M et al., 2011;Chintagunta SR et al.,2017).

We report a case of bullous urticaria pigmentosa, which is a rare clinical manifestation and also an extreme form of cutaneous mastocytosis to raise awareness about the differential diagnosis of vesicle and bullae in the infancy period.

2 CASE

A four-month-old boy was referred to our hospital presented with multiple patches and blisters, which began on the second day after birth. The lesions were first observed on the trunk and spread to the scalp and limbs within several days. The lesions started as erythematous patches all over his body, and several evolved to the vesicle. The vesicles were easily ruptured and became scars. He was the second child, and his brother was healthy. His birth and development were normal. He was breastfed and supplemented with formula. There was no history of drug ingestion both in mother and patient — no current episode of facial flushing, dyspnea, and diarrhea.

On physical examination, there were erythematous and hyperpigmentation plaques, vesicles, and erosions covered by crust (Figure 1). No lymph node enlargement found. Darier's sign was negative. At the first visit, gram staining from the erosions revealed moderate numbers of leukocytes and Gram-positive coccus.

Laboratory examination revealed mild microcytic hypochromic anemia (hemoglobin 11.9 g/dL, MCV 91.1 fL, and MCH 32 pg). Histopathology examination revealed rete ridges elongation of the epidermis and dermal perivascular and interstitial infiltration of lymphocytes, histiocytes, neutrophils, and mast cell, which came to a conclusion as cutaneous mastocytosis (Figure 2).

The patient was given topical antibiotics for a short period of time due to secondary infection on several lesions and oral cetirizine to reduce the symptoms. The patient was also referred to the Pediatric Department to find systemic involvement of mastocytosis. Bone marrow studies were not done due to parents' disapproval. In one month follow up period, the patient showed a slower progression of new lesions. No systemic symptoms reported. However, education and counseling about the possibility of systemic mastocytosis include the symptoms are done to prevent life-threatening systemic involvement.

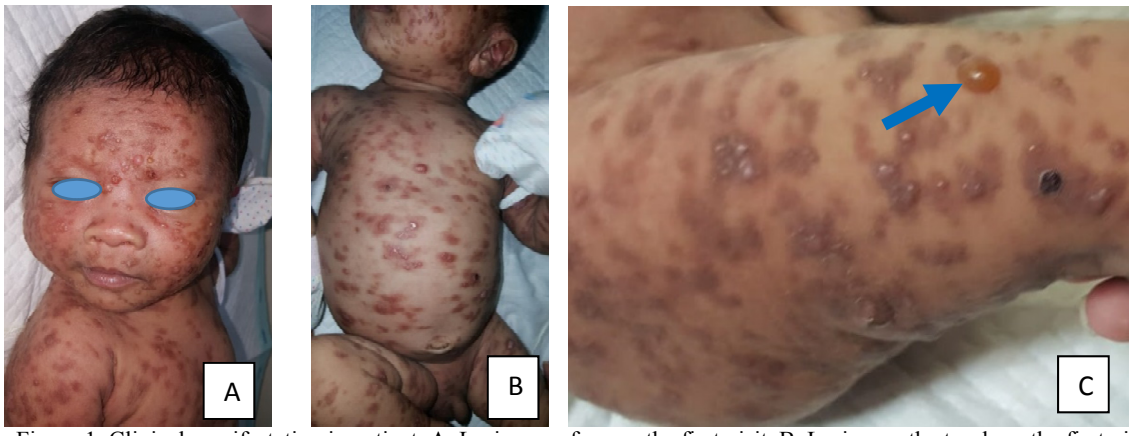

Figure 1. Clinical manifestation in patient. A. Lesions on face on the first visit, B. Lesion on the trunk on the first visit, C. Bullae on the right thigh (blue arrow).

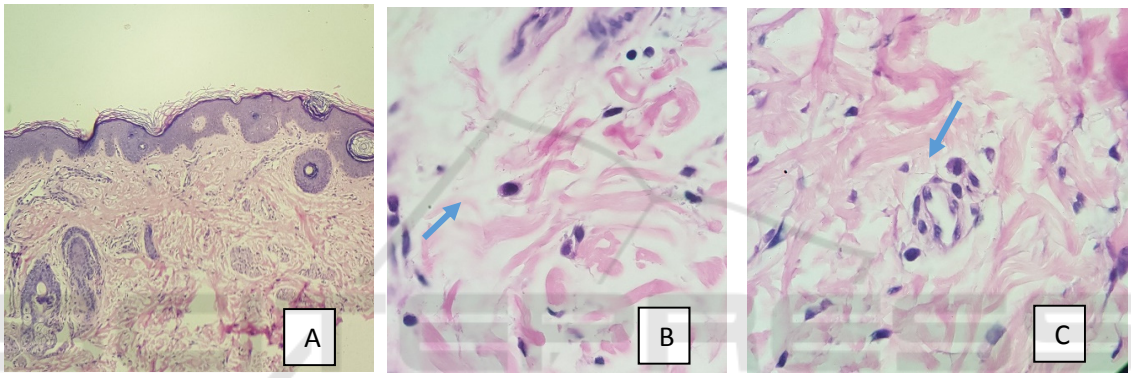

Figure 2. Histopathology findings. A. Epidermal rete ridges elongation (H&E,10x), B. Interstitial mast cell infiltration (blue arrow, H&E, 100x), C. Perivascular mast cell infiltration (blue arrow, H&E, 100x)

3 DISCUSSION

There are many conditions which manifest as a blister in the neonatal period. They can be caused by infectious, traumatic, or inherited causes. Infectious causes include bullous impetigo, staphylococcal scalded skin syndrome, neonatal varicella, candidiasis, etc.; meanwhile, non-infectious causes include epidermolysis bullosa, epidermolytic ichthyosis, incontinentia pigmenti, cutaneous mastocytosis, Langerhans cell histiocytosis or chronic bullous disease of the childhood.(Park MN et al., 2014).

The diagnosis was established by excluding other differential diagnoses. Since there was no sign of infection, infectious etiologies were excluded. The discrete distribution of lesion which was located on non-traumatic region excluded epidermolysis bullosa. Epidermolysis ichthyosis and incontinentia pigmenti were excluded due to the difference in the nature of the disease. Lastly, we excluded other types of cutaneous mastocytosis. The clinical entity which mimics initial clinical presentation, in this case, is diffuse cutaneous mastocytosis. Diffuse cutaneous mastocytosis (DCM) can be manifested initially as two types: one with a minimal blistering and large area of nodular and leathery skin and one with extensive blistering and/or exfoliation, usually accompanied by erythrodermic appearance. (Tharp MD et al., 2012). Both features are not fulfilled in this case; therefore, DCM was excluded. Telangiectasia macularis eruptive perstants (TMEP) is the least common form of cutaneous mastocytosis and rarely manifests in childhood. The typical lesions are telangiectatic macules in a tan or brown background and may co-exist with urticaria pigmentosa. (Costa DLM et al., 2011). In this patient, there was no telangiectasia as well as telangiectatic macules, so TMEP was also excluded.

The pathogenesis of pediatric cutaneous mastocytosis is not well understood, and most children do not present with mutations of c-kit in bone

marrow mast cells. (Castells M et al., 2011) An earlier study by (Verzijl et al., 2007) found that a quarter of pediatric patients presenting urticaria pigmentosa had a D816V codon mutation. Unfortunately, genetic testing has not been available yet in Indonesia.

Blistering of urticaria pigmentosa may happen and is considered to be exaggerated of Darier's sign. This is caused by the release of a mediator (mainly chymase) upon mast cell degranulation, which binds and cleaves the dermo-epidermal junction (DEJ). The DEJ is slowly stabilizing over the first two years of life, resulting in a reduction of vesiculobullous lesion by the age of 3. (Briley LD et al., 2008)

In this case, the histopathology examination showed diffuse dermal infiltration of mast cells which verified the clinical diagnosis of urticaria pigmentosa. Due to the presence of vesicles and bullae, the patient was finally diagnosed as bullous urticaria pigmentosa.

We referred the patient to the Child Health Department to rule out systemic involvement. Physical examination revealed no mucosal lesion and no hepatosplenomegaly. Bone marrow cytomorphology study was planned to confirm if the mast cell count exceeded 20% of the nucleated cells in the bone marrow. In this case, bone marrow aspiration could not be performed due to parents' disapproval. (Kettelhut et al., 1989) reported that the initial evaluation of the bone marrow of 17 children where 15 had urticaria pigmentosa and two had diffuse cutaneous mastocytosis revealed no adult-type mast aggregates. This finding is indicating that in most cases, cutaneous mastocytosis in children does not involve internal organs which precludes the need for routine bone marrow aspiration. (Uzzaman also con et al.,) cluded that only the persistent disease might justify repeated bone marrow examination aggressive systemic therapy. The clear majority of cases could be managed satisfactorily by symptomatic treatment. (Uzzaman A et al., 2000)

Management includes alleviation of the symptoms and avoidance of potential mast cell degranulating stimuli such as several drugs, food, local or systemic anesthetics, heat, as well as friction.(Asati DP et al., 2014).Patient was prescribed oral cetirizine daily. Parents have been adhering to periodic follow-up evaluation for the past two months, and up to now our patient responded well to oral antihistamines and had gradual reduction in new lesions (both blisters and papules) development.

Although pediatric cutaneous mastocytosis is generally benign and rarely involve other organs, parents were counseled in detail about the possibility of systemic involvement, the sign and the symptoms of systemic involvement. Whole-body flushing, shortness of breath, diarrhea may happen due to mast cell mediator release.

Systemic mastocytosis in children is extremely rare, and usually, the clinical symptoms could be managed by medication. The majority of these lesions and the severity of the symptom will resolve over time. However, it is essential to do regular follow up to detect systemic involvement.(Asati DP et al., 2014;Briley LD et al., 2008)

4 CONCLUSION

It could be concluded that dermatologist should remain aware of varied forms of pediatric cutaneous mastocytosis because of its rarity. Diagnosis of bullous urticaria pigmentosa should be thought in the infant with lesions suspected as urticaria pigmentosa accompanied by vesicle or bullae. Skin biopsy became mandatory to build the diagnosis. Systemic involvement screening, appropriate treatment, and follow up are required as routine. Finally, education and counseling also play an important role in the management of this entity.

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