Bullous mastocytosis in a 3-month-old infant

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ABSTRACT

Mastocytosis is a rare myeloid neoplasm characterized by abnormal proliferation and accumulation of mast cells in one or more organ systems including the skin, bone marrow, liver, spleen, lymph nodes and gastrointestinal tract. An infant presenting with bullous lesions is an even rarer clinical presentation of cutaneous mastocytosis. The symptoms and complications are mostly in proportion to the mast cell degranulation in tissues. Management is focused on preventing and treating this event. We report a three-month-old infant with bullous mastocytosis to enhance awareness about this rare diagnosis.

Key words: Infantile bullous mastocytosis, mast cells, urticaria pigmentosa

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INTRODUCTION

Mastocytosis is a heterogeneous group of myeloid neoplasms displaying abnormal proliferation and accumulation of mast cells in one or more organ systems including the skin, bone marrow, liver, spleen, lymph nodes and gastrointestinal tract.[1-3] It may be associated with a mutation in the gene encoding the c-kit receptor. The cutaneous forms include urticaria pigmentosa (UP), mastocytomas, diffuse cutaneous and telangiectasia macularis eruptiva perstans in their order of their frequency. It is difficult to determine the incidence of cutaneous mastocytosis (CM) due to its rarity, self-limiting nature in many cases and reluctance in reporting. Some authors have extrapolated a frequency of about 5-10 new cases per million population and about one in every 1000-8000 dermatology out-patients.[4,5] Bullous mastocytosis is even rarer form of diffuse CM, most often associated with its generalized form.[3] Other rarer variants include xanthelasma or pseudoxanthomatous forms.[6] Nearly two-thirds of the cases of UP have onset in infancy. Herein we report a rare case of bullous mastocytosis in a 3-month-old infant.

CASE REPORT

This exclusively breastfed male child presented with multiple asymptomatic, brownish macules, plaques and vesico-pustular lesions over the whole body. The baby was asymptomatic until 10 days of life, when his mother noted fluid filled and crusted papules over the scalp. He was given oral and topical antibiotics without any improvement, and new lesions appeared in a generalized distribution over the next few weeks. Furthermore, multiple brownish macules and plaques were observed *de novo* on the trunk and also at the sites of healed vesicular lesions [Figures 1 and 2]. Many of these plaques showed episodes of renewed activity in the form of bullous lesions that sometimes turned hemorrhagic over time [Figure 3]. The parents did not observe any change in the lesions associated with rubbing of the skin or with temperature change. The child was not irritable and there were no symptoms suggestive of gastrointestinal upset, breathing difficulty, flushing, hemodynamic disturbance or failure to thrive. There was no significant antenatal history except that of oligamnios at 36 weeks necessitating cesarean section with a slightly low birth weight baby. The child had normal weight gain after birth and was weighed 8 kg at the time of presentation, normal for his age. He was the only sibling and the parents or other family members had no similar illness ever.

On examination, the child was comfortable and alert, general physical and systemic examination revealed no apparent abnormality clinically. There was no evidence of hepatosplenomegaly or lymphadenopathy. The mucocutaneous examination showed generalized involvement in the form of multiple, discrete, brownish macules and slightly raised plaques with velvety or nevoid

surface of various shapes and size ranging from 0.5 to 3 cm. These lesions were interspersed with multiple vesicular, bullous, pustular or erosion-crusts, few of them surmounting the brownish background macules or plaques. Some of the bullae were hemorrhagic. There was no scarring, alopecia, milia formation, nail dystrophy or mucosal involvement. Darier's sign could be elicited on rubbing the skin lesions. We considered CM as a strong possibility owing to typical morphology and positive Darier's sign. However, because of absence of itching and unusual widespread involvement, congenital epidermolysis bullosa was considered as a differential diagnosis despite there being no predilection for the appearance of lesions at trauma-prone sites. Congenital syphilis and non-Langerhans cell histocytosis were other important clinical differentials. Routine hematological and biochemical profiles were within normal limits. The maternal serum Venereal Disease Research Laboratory (VDRL) test was nonreactive. Tzanck smear from the lesion was negative for acantholytic cells. A punch biopsy taken from a plaque over the forearm revealed a subepidermal split and dense infiltrate of monomorphic mast cells throughout the papillary, upper and mid reticular dermis [Figure 4a and b]. Cells stained strongly positive for Giemsa stain [Figure 5a and b]. A few extracellular mast cells granules were also seen. A final diagnosis of bullous CM was made.

DISCUSSION

It is important to differentiate between CM, systemic mastocytosis (SM) and localized mastocytomas as their clinical behaviors and long-term outcome are diverse.[1,2,7] The recent World Health Organization (WHO) classification (2008) defines major categories as CM, SM (indolent, aggressive and associated with clonal hematological non-mast cell lineage disease), mast cell leukemia (MCL), mast cell sarcoma and an extremely rare third major category of localized extracutaneous mastocytomas[8] [Table 1]. The diagnosis of CM is based on the clinical and histological findings in the skin together with the absence of criteria that would allow the diagnosis of SM. The definitive WHO diagnosis of SM requires the presence of one major and one minor criteria; or three minor criteria. These are described in Table 2.[9]

Peripheral total and differential blood counts were in normal range in our patient. 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 reluctance of the parents. However, they have been adhering to periodic follow-up evaluations for past six months and in the meantime, the patient could be successfully maintained on conservative treatment alone without the appearance of any systemic symptoms. Parents were counseled in detail about the preventive measures related to baby care and drug avoidance. Symptomatic control could be achieved by use of antihistamines and topical mid-potent corticosteroid creams.

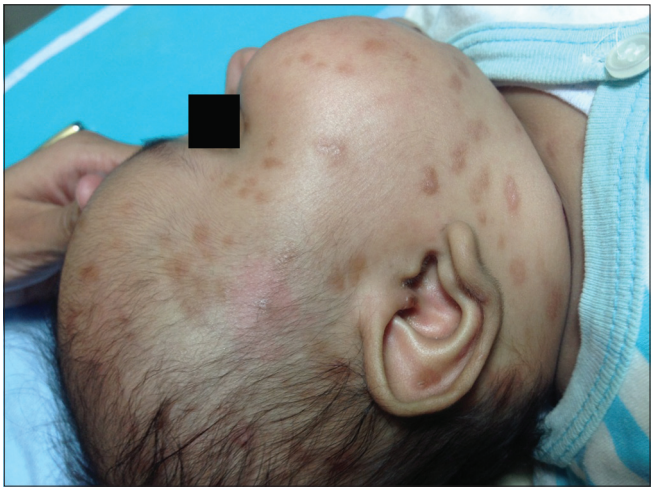

Figure 1: Brownish macules, tiny pustules and post-inflammatory changes

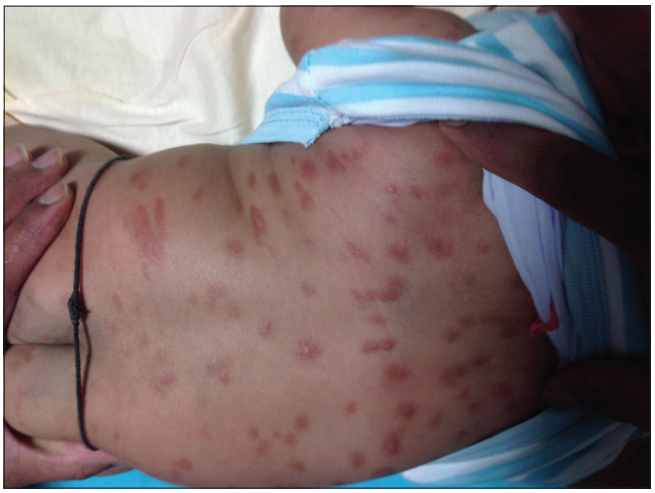

Figure 2: Generalized involvement seen on trunk

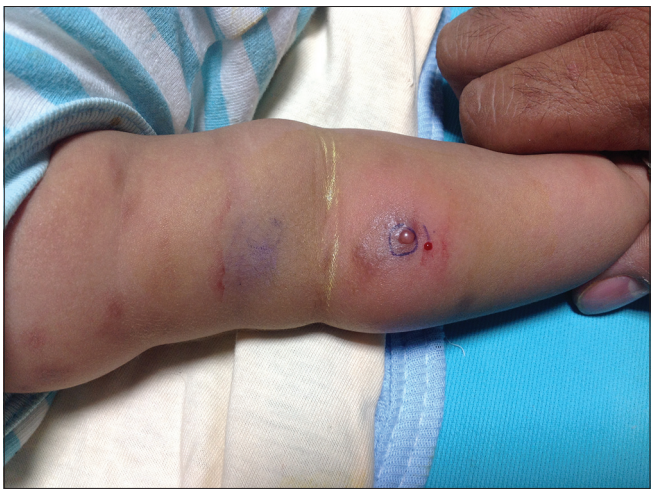

Figure 3: Typical hemorrhagic blisters

The prognosis and complications of cutaneous or indolent SM is definitely much better than aggressive systemic or leukemic variants. The important issues encountered in systemic variants, i.e. cytopenias, ascites, gastrointestinal disturbances, malabsorption, organomegaly, osteolysis, hemodynamic instability and malignant (leukemic) transformation are rarely associated with the cutaneous form.[2,10] However, there have been reports of internal organ involvement in disease apparently limited to skin only. These can range from mild derangements like disturbed liver function tests to potentially life-threatening hemodynamic complications. The treating physician should therefore actively search for any probable systemic associations based on clinical clues in the individual case.[10,11] Extensive blistering, large surface area involved and high serum total tryptase level could be important markers for systemic involvement.[12,13] These subtypes are also more prone for sudden death due to risk of sudden and massive mast cell degranulation which can lead to serious complications such as anaphylaxis, bronchoconstriction or cardiovascular collapse even after a small provocating factor like an insect bite or exposure to histamine releasing anesthetic agent. These possibilities must always be explained in detail to the patients' parents also.

Management of a patient with mastocytosis include alleviation of the symptoms and avoidance of potential mast cell degranulating stimuli such as heat, friction, sunlight, narcotics, alcohol, anticholinergic preparations, aspirin and other non-steroidal anti-inflammatory drugs, polymyxin B, local or systemic anesthetics and poisons like hymenoptera venom or bee bite.[3,14] For control of symptoms, antihistamines, sodium chromoglycate, acetyl salicylic acid and ketotifen are used as needed in individual case. Topical steroids, photochemotherapy, topical tacrolimus or pimecrolimus, topical miltefosine or intralesional injections of corticosteroids may also be useful.[14-16] Second-generation and newer tyrosine kinase inhibitors (e.g. dasatinib and midostaurin [PKC412]) are potential therapeutic options, which might have promising activity in SM cases. Hematopoietic stem cell transplantation may induce remission in selected cases with advanced SM (i.e. aggressive SM and MCL).[17] Our patient responded well to oral antihistamines and topical steroid and had gradual reduction in blistering and erosions.

Table 1: WHO classification (2008) of mastocytosis variants

Variant term	Subvariant
CM	UP
	MPCM
	DCM
	Mastocytoma of the skin
ISM	SSM
	Isolated BMM
SM-AHNMD/SM-AHD	SM-acute myeloid leukemia
	SM-myelodysplastic syndromes
	SM-chronic myelomonocytic leukemia
	SM-non-Hodgkins lymphoma
	SM-myeloproliferative disease
	SM-hypereosinophilic syndrome
ASM	
MCL	Leukemic MCL
Mast cell sarcoma	
Extracutaneous mastocytosis	

CM: Cutaneous mastocytosis, ISM: Indolent systemic mastocytosis, MPCM: Maculopapular cutaneous mastocytosis, DCM: Diffuse cutaneous mastocytosis, SSM: Smoldering systemic mastocytosis, BMM: Bone marrow mastocytosis, ASM: Aggressive systemic mastocytosis, MCL: Mast cell leukemia, SM-AHNMD: Systemic mastocytosis with an associated clonal hematological non-mast cell lineage disease, WHO: World Health Organization, UP: Urticaria pigmentosa, SM: Systemic mastocytosis

Table 2: WHO criteria for systemic mastocytosis

Major criterion
The presence of multifocal dense aggregates of >15 mast cells as detected with tryptase or other special stains in bone marrow or other extracutaneous organs
Minor criteria
Atypical morphology or spindle shapes in >25% of the mast cells in bone marrow sections, bone marrow aspirate, or other extracutaneous tissues
Mutational analysis of KIT showing a codon 816 mutation (e.g., Asp816Val) in bone marrow, blood, or extracutaneous organs
Bone marrow or other extracutaneous mast cells expressing the surface markers CD2, CD25, or both
Baseline serum tryptase levels >20 ng/mL (this criterion does not apply to patients with AHNMD)

AHNMD: Associated clonal hematological non-mast cell lineage disease, WHO: World Health Organization

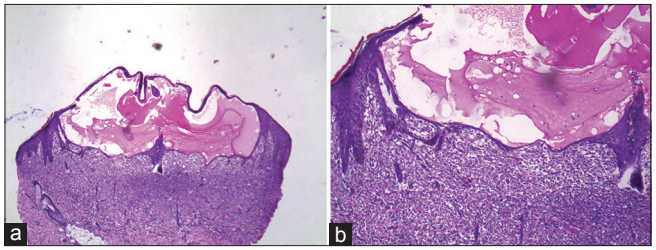

Figure 4: (a) Subepidermal split in scanning view. (H and E, ×20) (b) Mast cells densely filling the dermis below the blister (H and E, ×200)

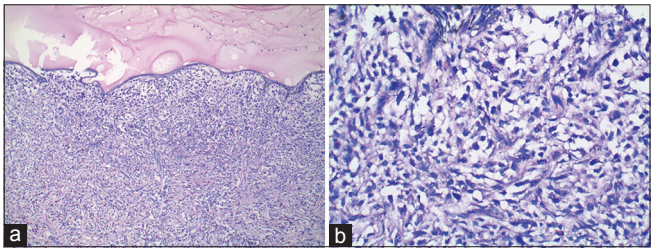

Figure 5: (a) Positive Giemsa stain. (×200) (b) Giemsa stain: Higher magnification (×400)

The debate between more and less aggressive management options for pediatric CM continues. However, since most of the case of pediatric mastocytosis resolve over time partially or completely, only the persistent disease may justify repeated bone marrow examination and aggressive systemic therapy. The vast majority of cases could thus be managed satisfactorily by symptomatic treatment alone.[18]

It could be concluded that pediatricians and dermatologists should remain aware of varied forms of CM because of its rarity and the distinctive management of each individual case.

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