Bullous cutaneous mastocytosis, a rarely reported disease in Asian children

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Summary

Diffuse cutaneous mastocytosis, the most rare form of cutaneous mastocytosis, often manifests as bullous lesions. Although cutaneous mastocytosis should be included in a differential diagnosis for pruritic skin lesions in children, early diagnosis of the disease is not easy due to its rare occurrence. A 17-month-old boy presented with recurrent itchy bullous skin lesions. He had been treated as atopic dermatitis at other hospitals for about one year, however, he was eventually diagnosed with diffuse cutaneous mastocytosis through skin biopsy. Unlike adults, children with cutaneous mastocytosis usually improve with age and do not develop systemic mastocytosis. Therefore, early and accurate diagnosis of cutaneous mastocytosis in children is essential for appropriate care. *(Asian Pac J Allergy Immunol 2014;32:354-7)*

Keywords: *cutaneous mastocytosis, exanthema, blister, pruritus, child*

Introduction

Mastocytosis is characterized by an abnormally increased mast cell infiltration of skin and extracutaneous organs.[1,2] Cutaneous mastocytosis (CM) is defined as mast cell infiltration limited to the skin.[1] CM manifests as a variety of skin lesions, including maculopapular rash, nodules, plaques, bullae and diffuse skin erythema,[3,4] and can be distinguished from many other conditions with similar findings, including atopic dermatitis, staphylococcal scalded skin syndrome, bullous impetigo, epidermolysis bullosa, erythema multiforme, toxic epidermal necrolysis and incontinentia pigmenti.[5-8] Despite this varied presentation, a diagnosis of CM in children is often low on the differential diagnosis due to its rare occurrence. We report a child who presented with recurrent bullous skin lesions. He was preliminarily diagnosed with atopic dermatitis and superimposed bullous impetigo, but skin biopsy eventually revealed a diagnosis of diffuse cutaneous mastocytosis (DCM).

Case description

A 17-month-old boy visited our hospital with multiple bullae on his scalp, trunk and extremities and desquamation on his abdomen. The skin lesions were accompanied by itching. These lesions had been intermittently repeated and treated as atopic dermatitis since 6 months of age. There was no significant family medical history. On admission, vital signs were as follows: body temperature 37.7°C, heart rate 130 beats/minute and respiratory rate 30 breaths/minute. On physical examination, diffuse skin erythema with multiple papules and bullae distributed on the scalp, trunk and extremities, and desquamation was observed on the abdomen (Figure 1). Chest and abdomen examinations were unremarkable, and there was no hepatosplenomegaly or lymphadenopathy. Laboratory findings revealed the following results: white blood cell count 16,780/μL (neutrophils 28.8%, lymphocytes 62.3%, eosinophils 1.0%), hemoglobin 11.4 g/dL, platelet count 484,000/μL, aspartate transaminase 37 U/L, alanine transaminase 12 U/L, lactate dehydrogenase 705 U/L, total bilirubin 0.23 mg/dL, erythrocyte sedimentation rate 19 mm/hr and C-reactive protein 2.11 mg/dL. We preliminarily diagnosed the child with atopic dermatitis and superimposed bullous impetigo based on his bullous skin lesions and previous history. We performed local therapy consisting of

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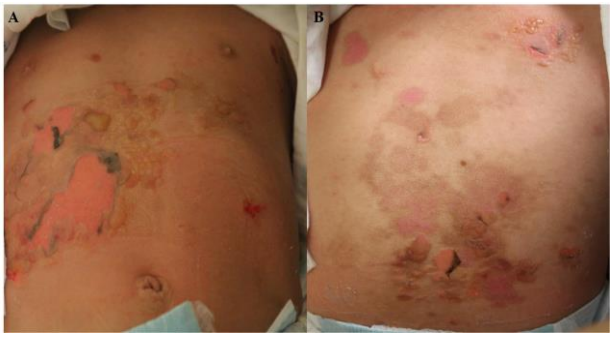

Figure 1. Diffuse cutaneous erythema with several bullae and desquamation. (A) Ventral aspect of the trunk and (B) dorsal aspect of the trunk.

daily wet dressings with mupirocin ointment and systemic antibiotic therapy consisting of intravenous amoxicillin/clavulanate and amikacin as well as oral roxithromycin. Oral chlorpheniramine and ketotifen were given to reduce itching. We considered other possible diagnoses because the recurrent and extensively distributed bullous skin lesions were unusual for both atopic dermatitis and impetigo. Accordingly, skin biopsy was performed on hospital day 3, and the pathologic findings were consistent with CM (Figure 2). Topical glucocorticoid (0.25% prednicarbate) and oral hydroxyzine were added on hospital day 6 due to continuing skin lesions and itching. Although the desquamation and itching began to improve, new papules developed on the scalp. For the new skin lesions, ranitidine, an H2 antihistamine, and oral prednisolone (1 mg/kg/day) were added on hospital day 8. On hospital day 11, bacterial culture of the desquamated skin grew methicillin-resistant *Staphylococcus aureus* (MRSA), and intravenous amikacin was changed to intravenous arbekacin. The newly-developed skin lesions disappeared, and itching was controlled with the aforementioned treatment. The child was discharged from the hospital on day 14. Laboratory results including negative D816V point mutation of *c-kit* gene and elevated serum tryptase level to 67.3 ng/mL (normal range: 1.9-13.5 ng/mL) were reported after the discharge. During outpatient follow-up, oral prednisolone was stopped after completion of a 14-day course, and maintenance treatment was initiated with ketotifen and montelukast. Ten months have passed since the diagnosis of DCM, and the patient has not showed any systemic symptoms or signs consistent with

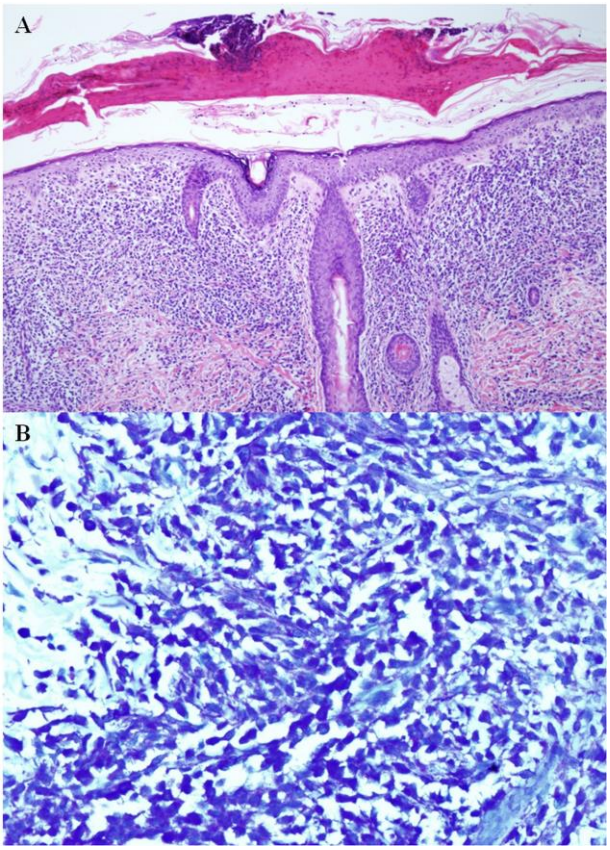

Figure 2. Microscopic findings of the biopsied skin show diffuse mast cell infiltration of the upper dermis. (A) H&E, x100 and (B) Toluidine blue, x400.

systemic mastocytosis until now. However, his itching sensation and skin erythema have waxed and waned without bullae formation.

Discussion

Mastocytosis is divided into CM and systemic mastocytosis (SM) based on clinical presentation, extracutaneous organ involvement and pathologic findings according to the World Health Organization classification.[2,9] CM is defined as mastocytosis limited to the skin, while SM is defined by involvement of other organs, such as bone marrow, liver, spleen and lymph nodes.[2] CM is further divided into maculopapular cutaneous mastocytosis (MPCM), solitary mastocytoma, or DCM based on the characteristics of the skin lesions.[2,9] MPCM, also known as urticaria pigmentosa, manifests as multiple red, brown or yellow macules and nodules and is the most common type, occupying in 65-90% of CM cases in children.[1,3,4,9-11] Mastocytoma has a prevalence of

10-35% of CM cases in children and manifests as solitary nodules or masses which are larger than those seen in MPCM.[1,3,4,9-11] DCM is the most rare type of CM in children (1-8% of cases) and manifests as extensive skin lesions over the scalp, trunk, and extremities, with occasional bullae.[1,3,4,6,9,12] Mastocytosis is also classified into two groups according to age of occurrence: childhood-onset and adult-onset.[2] Adult-onset mastocytosis tends to progress to SM with a poor prognosis, whereas childhood-onset mastocytosis seldom progresses to SM and tends to improve during adolescence.[1,2,4,10] Due to the benign nature of CM in children, a bone marrow study to evaluate possible SM is generally not necessary.[1,4,9] One report has shown a child who died of SM which evolved from DCM,[13] and recent reports on long-term observations of children with CM have shown that partial improvement of CM is more common than complete resolution.[4,6,10] Therefore, a bone marrow study is recommended when CM patients develop symptoms or signs consistent with SM or their serum tryptase level persists above 20 ng/mL.[1,6,9]

Symptoms and signs of childhood-onset CM appear within 1 year of life in 90% of patients,[3,4,12] and are caused by increased mast cells degranulation.[1,2] Mast cells release histamine, serotonin, leukotrienes, prostaglandins and cytokines,[2,14] and these substances cause skin manifestations (itching, flushing, redness, swelling), abdominal symptoms (abdominal pain, vomiting, diarrhea), respiratory symptoms (cough, dyspnea), and hypotension or anaphylaxis in extreme cases.[1,2,9,10,15] These symptoms resemble those of atopic dermatitis which is more frequently diagnosed in children, and clinicians may confuse the two diseases. The severity of the mediator-related symptoms and skin infiltration tends to correlate with serum tryptase level.[4,9,15] Our patient presented with skin lesions and symptoms at 6 months of age, suffered from recurrent episodes without an accurate diagnosis, and eventually was diagnosed with DCM at 17 months of age. Because he did not show any manifestations consistent with SM on physical or laboratory examination, we did not perform a bone marrow study.

Treatment for CM is primarily aimed at alleviating mast cell mediator-related symptoms. Cytoreduction therapy against the increased mast cells is only recommended in patients with severe forms of SM refractory to other therapies because of its severe complications, such as immune suppression and pancytopenia.[1,14] H1 and H2 antihistamines, cromolyn sodium and ketotifen are used to reduce the mediator-related symptoms, and glucocorticoids may be effective for severe symptoms.[1,9] Combination therapy with two or more drugs should be considered for patients with severe symptoms or symptoms refractory to a single drug.[1,9] In addition, patients should avoid triggers that provoke mast cell activation and degranulation.[1] Various types of physical stimuli, such as heat, cold, sudden temperature change, friction or pressure, and emotional stimuli, such as stress and anxiety, may be triggers.[1,10] Various drugs, such as non-steroidal anti-inflammatory drugs (ibuprofen, diclofenac), opioids (morphine, codeine, meperidine), sedatives (ketamine), cough medications (dextromethorphan, dimemorfan), antibiotics (vancomycin, clindamycin), polyvitaminic complexes, enhancing contrast media and volatile anesthetics as well as viral or bacterial infections may also trigger mast cell activation and degranulation.[1,4,14,15] Trigger foods, including prawns, bananas, kiwi, tomatoes, pork ribs, bread rolls, eggs and chocolate were also reported.[15] Local skin care with moisturizers and prevention and treatment of secondary bacterial skin infections are also important.[1] In our patient, initial H1 antihistamine (chlorpheniramine) and ketotifen therapy did not improve skin lesions and itching. Then, another H1 antihistamine and topical glucocorticoid were added. With continued development of new skin lesions, oral glucocortidoid therapy was added and the child's symptoms and signs improved. He also developed a secondary skin infection with MRSA and was treated with parenteral antibiotics.

In conclusion, DCM in children is a benign condition that generally improves during adolescence. Unfortunately, inaccurate initial diagnosis and treatment may lead to unnecessary suffering. The disease's rare occurrence and physicians' lack of experience may lead to these initially poor outcomes. A diagnosis of CM should be considered in children with multiple maculopapular or bullous skin lesions. Furthermore, this case demonstrates that physicians should not hesitate to perform skin biopsy of skin lesions to establish an accurate diagnosis.

References

1. Castells M, Metcalfe DD, Escribano L. Diagnosis and treatment of cutaneous mastocytosis in children: practical recommendations. Am J Clin Dermatol. 2011;12:259-70.
2. Sperr WR, Valent P. Diagnosis, progression patterns and prognostication in mastocytosis. Expert Rev Hematol. 2012;5:261-74.
3. Kiszewski AE, Durán-Mckinster C, Orozco-Covarrubias L, Gutiérrez-Castrellón P, Ruiz-Maldonado R. Cutaneous mastocytosis in children: a clinical analysis of 71 cases. J Eur Acad Dermatol Venereol. 2004;18:285-90.
4. Lange M, Niedoszytko M, Renke J, Glén J, Nedoszytko B. Clinical aspects of paediatric mastocytosis: a review of 101 cases. J Eur Acad Dermatol Venereol. 2013;27:97-102.
5. Oranje AP, Soekanto W, Sukardi A, Vuzevski VD, van der Willigen A, Afiani HM. Diffuse cutaneous mastocytosis mimicking staphylococcal scalded-skin syndrome: report of three cases. Pediatr Dermatol. 1991;8:147-51.
6. Lange M, Niedoszytko M, Nedoszytko B, Lata J, Trzeciak M, Biernat W. Diffuse cutaneous mastocytosis: analysis of 10 cases and a brief review of the literature. J Eur Acad Dermatol Venereol. 2012;26:1565-71.
7. Lee EH, Kim MR, Kang TW, Kim SC. Diffuse cutaneous mastocytosis with generalized bullae. Ann Dermatol. 2010;22:77-80.
8. Kleewein K, Lang R, Diem A, Vogel T, Pohla-Gubo G, Bauer JW, et al. Diffuse cutaneous mastocytosis masquerading as epidermolysis bullosa. Pediatr Dermatol. 2011;28:720-5.
9. Torrelo A, Alvarez-Twose I, Escribano L. Childhood mastocytosis. Curr Opin Pediatr. 2012;24:480-6.
10. Middelkamp Hup MA, Heide R, Tank B, Mulder PG, Oranje AP. Comparison of mastocytosis with onset in children and adults. J Eur Acad Dermatol Venereol. 2002;16:115-20.
11. Ben-Amitai D, Metzker A, Cohen HA. Pediatric cutaneous mastocytosis: a review of 180 patients. Isr Med Assoc J. 2005;7:320-2.
12. Heide R, Zuidema E, Beishuizen A, Den Hollander JC, Van Gysel D, Seyger MM, et al. Clinical aspects of diffuse cutaneous mastocytosis in children: two variants. Dermatology. 2009;219:309-15.
13. Murphy M, Walsh D, Drumm B, Watson R. Bullous mastocytosis: a fatal outcome. Pediatr Dermatol. 1999;16:452-5.
14. Metcalfe DD. Mast cells and mastocytosis. Blood. 2008;112:946-56.
15. Alvarez-Twose I, Vañó-Galván S, Sánchez-Muñoz L, Morgado JM, Matito A, Torrelo A, et al. Increased serum baseline tryptase levels and extensive skin involvement are predictors for the severity of mast cell activation episodes in children with mastocytosis. Allergy. 2012;67:813-21.