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A widespread blistering eruption: diffuse cutaneous mastocytosis

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Abstract

Diffuse cutaneous mastocytosis with bullous formation is a rare childhood disease. We report a 5-month-old male who presented with a 3-week history of cutaneous bullae and pruritus. On examination, he had erythema of the cheeks bilaterally and diffuse slightly hyperpigmented, indurated skin on his trunk and abdomen. There were tense vesicles, bullae, and erosions linearly arranged on his trunk and extremities. Both the laboratory and imaging workup were normal. Subsequently, a punch biopsy of a vesicle on the abdomen was obtained and findings confirmed a diagnosis of diffuse cutaneous mastocytosis. An EpiPen® was prescribed due to the slightly increased anaphylaxis risk compared to other forms of mastocytosis. There are many purported triggers of diffuse cutaneous mastocytosis and there is currently no known cure which makes management of this disease challenging. This case highlights a rare condition for which official treatment guidelines do not exist. A prompt dermatologic diagnosis is necessary to ensure proper workup and regulation is in place.

Keywords: bullae, cutaneous, mast cell, mastocytosis, pediatric

Introduction

Diffuse cutaneous mastocytosis (DCM) is characterized by abnormal mast cell hyperplasia within the skin [1]. It is usually seen in children within the first year of life with a slight male predominance [2]. The disease is believed to be due to various activating mutations in the *c-KIT* gene [3]. The pathogenesis involves widespread mast cell degranulation, which produces systemic symptoms such as flushing, pruritus, diarrhea, and abdominal pain [2]. The release of tryptase from these cells leads to separation of the dermis and epidermis resulting in blister formation. This disease clinically presents as leathery *peau d'orange* skin along with the manifestation of widespread, tense, and sometimes hemorrhagic blisters [2]. Additionally, many patients with mastocytosis will present with a positive Darier sign, the appearance of a wheal and flare reaction after slightly stroking affected skin [4].

Case Synopsis

A 5-month-old presented to clinic for evaluation of a 3-week history of cutaneous bullae and pruritus. The patient was initially prescribed cephalexin in the emergency department for presumed bullous impetigo and symptoms partially improved, but he subsequently flared. Review of systems was positive for flushing of the cheeks without associated shortness of breath, diarrhea, and vomiting. Vital signs were within normal limits. Physical examination revealed erythema of the cheeks bilaterally and diffuse slightly hyperpigmented, indurated skin on his trunk and abdomen. There

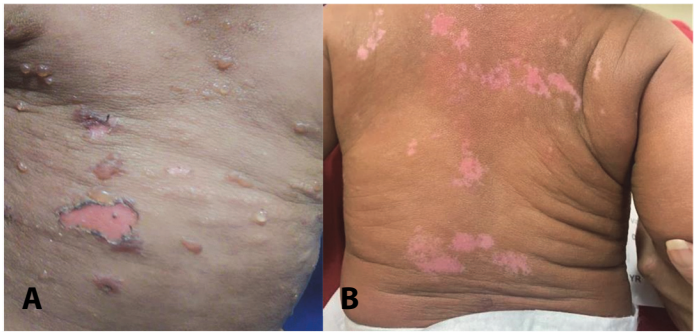

Figure 1. ***A)*** *Diffuse vesicles, bullae, and erosions arranged in a linear fashion on the abdomen and trunk.* ***B)*** *Dyspigmented macules and patches at the sites of previous blisters appearing on the back.*

were tense vesicles, bullae, and erosions linearly arranged on his trunk and extremities (**Figure 1A**). White macules and patches also appeared on his back (**Figure 1B**). Organomegaly was not present. Complete blood count, chemistry panel, and an abdominal ultrasound were normal with the exception of an elevated platelet count at 603x10 ^{9}/L (normal 244-529x10^{9}/L). Serum tryptase level was elevated at 86.9µg/L (normal <11). A punch biopsy of a vesicle on the abdomen was obtained and revealed a subepidermal blister with sheets of mast cells throughout the papillary and upper reticular dermis (**Figure 2A**). The mast cells were also highlighted by CD117 and tryptase stains (**Figures 2B, C**). The patient was started on daily cetirizine, given an epinephrine autoinjector, and referred to the National Institutes of Health (NIH) for further evaluation and management. The patient will join the NIH mastocytosis protocol when he qualifies at age 2. At that time, genetic testing for the *KIT* gene will take place. The child continues to experience ongoing pruritus and bouts of blistering.

Case Discussion

Although most cases of pediatric mastocytosis will resolve over time, DCM in those with higher baseline serum tryptase levels and an extensive amount of skin involvement may be associated with a prolonged course [5]. There is a small risk of anaphylaxis and death given the high mast cell burden [5]. The optimal workup to rule out bone marrow involvement and association with leukemia is not well-known among pediatric and dermatology practitioners given the rarity of the disease and lack of guidelines.

In contrast with adults, bone marrow involvement and associated leukemia is less common in pediatric patients. Based on a retrospective review of pediatric mastocytosis patients at the NIH, routine bone marrow biopsy in children with DCM is not recommended unless organomegaly is present and the information will impact therapeutic management [6]. This point is highlighted in our patient whose bone marrow biopsy was deferred. Negative peripheral mutational analysis for the *KIT* D816V mutation provides reassurance against systemic involvement in DCM patients but may also be negative in patients with systemic disease and a low allelic burden. Well-differentiated systemic mastocytosis is a condition in the differential diagnosis that also has an onset in infancy and skin manifestations similar to DCM. However, over time it leads to systemic symptoms. Bone marrow biopsy is positive for mast cell aggregation [7].

The risk of anaphylaxis in patients with cutaneous mastocytosis is not as high in children compared to adults. The exact risk is undefined but based on the

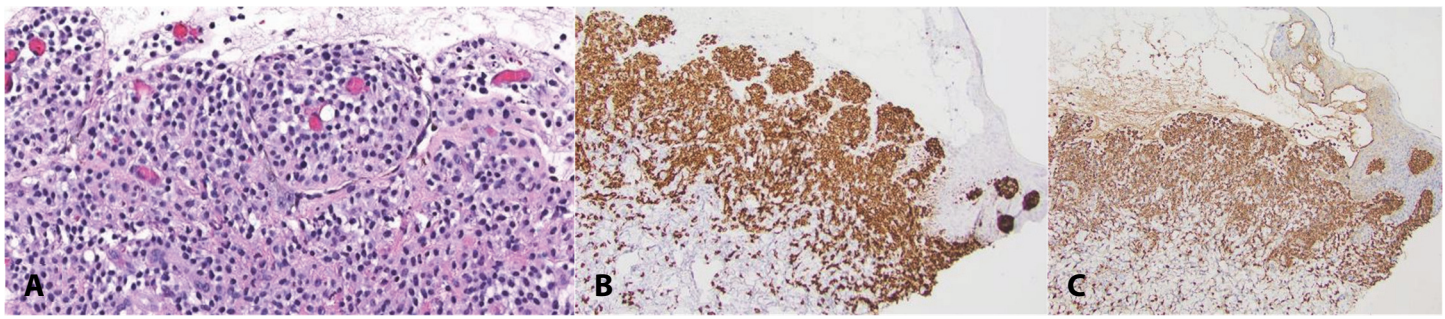

Figure 2. ***A)*** *Subepidermal blister with sheets of mast cells throughout the papillary and upper reticular dermis. H&E, 40×.* ***B)*** *Sheets of mast cells highlighted by CD117 stain, 20×.* ***C)*** *Sheets of mast cells highlighted by tryptase stain, 20×.*

experience of the mastocytosis group at the NIH, it may be lower than previously reported (1.5-9%) in the literature [8]. The most common trigger of anaphylaxis in pediatric DCM is idiopathic [9]. It is more likely in those with extensive skin involvement and high total serum tryptase levels [10]. However, a recent report stated that children with high total serum tryptase can experience flushing without the hemodynamic changes associated with anaphylaxis [10]. Stable mature tryptase levels could help rule out anaphylaxis risk in the setting of both a high total tryptase and severe skin involvement.

Management for DCM involves both trigger avoidance and prophylactic therapy. Some potential triggers for those with DCM include skin manipulation, temperature changes, vaccinations, and immunological stimuli such as infections (**Table 1**). Prevention involves use of corticosteroids, antihistamines, leukotriene receptor antagonists, and mast cell stabilizers like cromolyn sodium [11]. Corticosteroids are the preferred treatment for the more severe cases presenting with blister formation [11]. Long-acting anti-histamines are currently the mainstay of prophylactic treatment [12]. In the rare event that a DCM patient experiences acute cardiovascular collapse despite prophylaxis and carefully avoiding triggers, an epinephrine injection is the drug of choice to stabilize mast cells and prevent further degranulation [12].

Tyrosine kinase inhibitors (TKIs) are therapeutic options for systemic mastocytosis given this condition's frequent association with *KIT* mutations (*KIT* D816V being the most common). Imatinib, an inhibitor of wild-type KIT, PDGFR, and BCR-ABL, is currently FDA approved for systemic mastocytosis patients who lack a *KIT* D816V mutation or whose *KIT* mutation is unclear [13]. In contrast, apravitinib is FDA approved for the treatment of systemic mastocytosis in adult patients with the specific *KIT* D816V mutation [14]. Although not yet FDA approved due to a lack of clinical trials, there has been discussion about other TKIs that have the potential to treat systemic mastocytosis patients [13, 15]. Likely due to CM's typically benign course, the use of TKIs has not yet been studied in CM patients though the cutaneous lesions can be disfiguring and aggressive treatment may be appropriate in select cases.

Table 1. *Potential triggers of mast cell activation in diffuse cutaneous mastocytosis [11, 19, 20].*

Trigger	Examples
Mechanical and Physical Stimulation	Applied pressure, friction of skin lesions
Drugs	Opioids, aspirin, NSAIDS, vancomycin
Temperature	Heat, cold, or sudden changes in temperature
Diet	Spicy foods, histamine-containing foods (ie., aged cheese, spinach, eggplant), histamine-releasing foods (i.e., strawberries, nuts, shellfish)
Infections	Bacteria, parasites, viruses
Other	Emotional or physical stress, fever, irritability, teething, vaccinations, insect bites

NSAIDs, non-steroidal anti-inflammatory drugs.

Since 86% of childhood mastocytosis cases have also been associated with numerous kit mutations, this subset of patients could potentially benefit from TKI treatment [16]. Tyrosine kinase inhibitors especially could be helpful for DCM patients who progress to having systemic involvement [16]. The response to TKI treatment would depend on the patient's specific *KIT* mutation. A case report showed that imatinib 100mg daily improved lesion size and pruritus in a 23-month-old child with progressive CM [17]. A few other case reports have demonstrated success with imatinib in rapidly treating pediatric patients specifically with DCM [18].

Conclusion

Prevention of symptoms in DCM is challenging and involves avoiding triggers of mast cell degranulation such as heat, friction, venomous insect bites, and non-steroidal anti-inflammatory drugs. There is currently no known cure, but use of H1 and H2 antihistamines, topical and oral sodium cromoglycate, ketotifen, systemic and topical corticosteroids, and pimecrolimus have all been reported to be useful in alleviating symptoms [1]. The successful use of TKIs in patients with systemic

mastocytosis is promising for the future of DCM patients given this condition's similar association with *c-KIT* mutations. In addition, parents should be advised to carry an EpiPen® due to a slightly increased risk of anaphylaxis in DCM compared to other forms of mastocytosis. A prompt dermatologic diagnosis is crucial to ensure proper workup and management is in place.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Asati DP, Tiwari A. Bullous mastocytosis in a 3-month-old infant. *Indian Dermatol Online J*. 2014;5:497-500. [PMID: 25396140].
2. Nayak S, Acharjya B, Devi B, Behera SK. Bullous mastocytosis. *Indian J Dermatol*. 2007;52:201.
3. Hartmann K, Escribano L, Grattan C, et al. Cutaneous manifestations in patients with mastocytosis: Consensus report of the European Competence Network on Mastocytosis; the American Academy of Allergy, Asthma & Immunology; and the European Academy of Allergology and Clinical Immunology. *J Allergy Clin Immunol*. 2016;137:35-45. [PMID: 26476479].
4. Achehboune K, Elboukhari K, Baybay H, Elloudi S, Mernissi F. Bullous disease in infant: think of cutaneous mastocytosis. *PAMJ Clin Med*. 2020;2. [DOI: 10.11604/pamj-cm.2020.2.49.21265].
5. Alvarez-Twose I, Vañó-Galván S, Sánchez-Muñoz L, 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;67:813-821. [PMID: 22458675].
6. Carter MC, Clayton ST, Komarow HD, et al. Assessment of clinical findings, tryptase levels, and bone marrow histopathology in the management of pediatric mastocytosis. *J Allergy Clin Immunol*. 2015;136:1673-1679.e3. [PMID: 26044856].
7. Huang L, Wang SA, Konoplev S, et al. Well-differentiated systemic mastocytosis showed excellent clinical response to imatinib in the absence of known molecular genetic abnormalities. *Medicine (Baltimore)*. 2016;95 :e4934. [PMID: 27741105].
8. Matito A, Carter M. Cutaneous and systemic mastocytosis in children: a risk factor for anaphylaxis? *Curr Allergy Asthma Rep*. 2015;15:22. [PMID: 26139333].
9. Brockow K, Jofer C, Behrendt H, Ring J. Anaphylaxis in patients with mastocytosis: a study on history, clinical features and risk factors in 120 patients. *Allergy*. 2008;63:226-232. [PMID: 18186813**].**
10. Awan SF, Schwartz LB, Maric I, Metcalfe DD, Carter MC. Acute increases in total serum tryptase unassociated with hemodynamic instability in diffuse cutaneous mastocytosis. *Ann Allergy Asthma Immunol*. 2022;129:249-252. [PMID: 35568301].
11. Bankova LG, Walter JE, Iyengar SR, Lorenzo ME, Hornick JL, Castells MC. Generalized bullous eruption after routine vaccination in a child with diffuse cutaneous mastocytosis. *J Allergy Clin Immunol Pract*. 2013;1:94-96. [PMID: 24229828].
12. Otani IM, Carroll RW, Yager P, et al. Diffuse cutaneous mastocytosis with novel somatic KIT mutation K509I and association with tuberous sclerosis. *Clin Case Rep*. 2018;6:1834-1840. [PMID: 30214774].
13. Vaes M, Benghiat FS, Hermine O. Targeted Treatment Options in Mastocytosis. *Front Med (Lausanne)*. 2017;4:110. [PMID: 28775983].
14. Sumbly V, Landry I, Iqbal S, et al. The Role of Avapritinib for the Treatment of Systemic Mastocytosis. *Cureus*. 2021;13:e18385. [PMID: 34729266].
15. Piris-Villaespesa M, Alvarez-Twose I. Systemic Mastocytosis: Following the Tyrosine Kinase Inhibition Roadmap. *Front Pharmacol*. 2020;11:443. [PMID: 32346366].
16. Bodemer C, Hermine O, Palmérini F, et al. Pediatric mastocytosis is a clonal disease associated with D816V and other activating c-KIT mutations. *J Invest Dermatol*. 2010;130:804-815. [PMID: 19865100].
17. Hoffmann KM, Moser A, Lohse P, et al. Successful treatment of progressive cutaneous mastocytosis with imatinib in a 2-year-old boy carrying a somatic KIT mutation. *Blood*. 2008;112:1655-1657. [PMID: 18567837].
18. Morren MA, Hoppé A, Renard M, et al. Imatinib mesylate in the treatment of diffuse cutaneous mastocytosis. *J Pediatr*. 2013;162:205-207. [PMID: 23069194].
19. Rayinda T, Oktarina DAM, Danarti R. Diffuse cutaneous mastocytosis masquerading as linear IgA bullous dermatosis of childhood. *Dermatol Reports*. 2021;13:9021. [PMID: 33824710].
20. Czarny J, Lange M, Ługowska-Umer H, Nowicki RJ. Cutaneous mastocytosis treatment: strategies, limitations and perspectives. *Postepy Dermatol Alergol*. 2018;35:541-545. [PMID: 30618520].