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Management of Cutaneous Mastocytosis during Childhood: Update from the Literature

Çocukluk Döneminde Kutanöz Mastositoz Yönetimi: Literatürden Güncelleme

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Management of Cutaneous Mastocytosis during Childhood: Update from the Literature

Abstract

Cutaneous mastocytosis defines a group of diseases categorized by the existence of augmented numbers of mast cells in the dermis. Cases with cutaneous mastocytosis do not meet diagnostic conditions for systemic mastocytosis and demonstrate no proof of organ participation other than the dermis. This article after mentioning history, prevalence, and classification briefly reviews clinical features and triggers of mast cell activation and lastly discusses the management of cutaneous mastocytosis under the light of current observations in detail. Patients with cutaneous mastocytosis often be influenced by mast cell mediator-linked symptoms, which are often commenced by pressures on the dermal lesions. Management of cutaneous mastocytosis is chiefly built on avoiding triggers of mast cells. The availability of epinephrine autoinjectors in case of severe systemic reactions such as anaphylaxis and utilizing antihistamines when symptoms occur to establish the backbone of treatment in cutaneous mastocytosis cases.

Keywords: Children, cutaneous mastocytosis, mast cell, mastocytoma, pediatric mastocytosis, urticaria pigmentosa.

Özet

Kutanöz mastositoz, dermiste artan sayıda mast hücrelerinin varlığına göre kategorize edilen bir hastalık grubunu tanımlar. Kutanöz mastositozlu vakalar, sistemik mastositoz için tanısal koşulları karşılamaz ve dermis dışında herhangi bir organ katılımı kanıtı göstermez. Bu yazıda tarih, prevalans ve sınıflandırmadan bahsedildikten sonra mast hücre aktivasyonunun klinik özellikleri ve tetikleyicileri kısaca gözden geçirilmekte ve son olarak kutanöz mastositozun yönetimi güncel gözlemler ışığında detaylı olarak tartışılmaktadır. Kutanöz mastositozlu hastalar sıklıkla, dermal lezyonlar üzerindeki baskı/basınç ile tetiklenen mast hücre mediatörüne bağlı semptomlardan etkilenir. Kutanöz mastositozun yönetimi esas olarak mast hücre tetikleyicilerinden kaçınma üzerine kuruludur. Anafilaksi gibi şiddetli sistemik reaksiyonlar durumunda epinefrin otoenjektörlerinin mevcudiyeti ve semptomlar ortaya çıktığında antihistaminiklerin kullanılması kutanöz mastositoz vakalarında tedavinin temel unsurunu oluşturur.

Anahtar Sözcükler: Çocuklar, kutanöz mastositoz, mast hücresi, mastositoma, pediatrik mastositoz, ürtiker pigmentosa.

Introduction

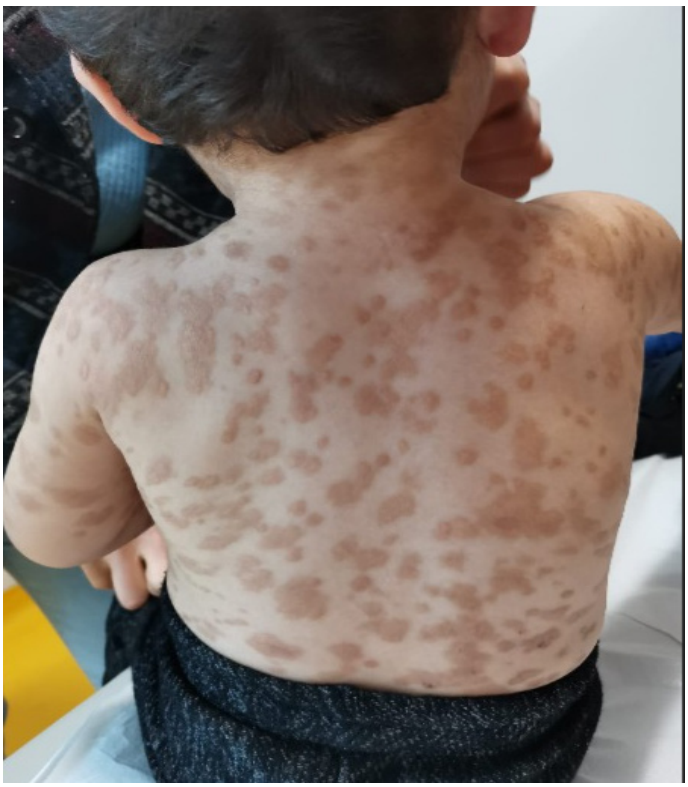
Cutaneous mastocytosis (CM) defines a group of diseases categorized by the existence of increased numbers of mast cells (MCs) in the dermis. Cases with CM do not meet diagnostic conditions for systemic mastocytosis and demonstrate no proof of organ participation other than the dermis (1).

This article after mentioning the history, prevalence, and classification of CM will review different clinical features and triggers of MC activation and lastly discusses the management of CM in children under the light of current literature in detail.

History, Prevalence, and Classification

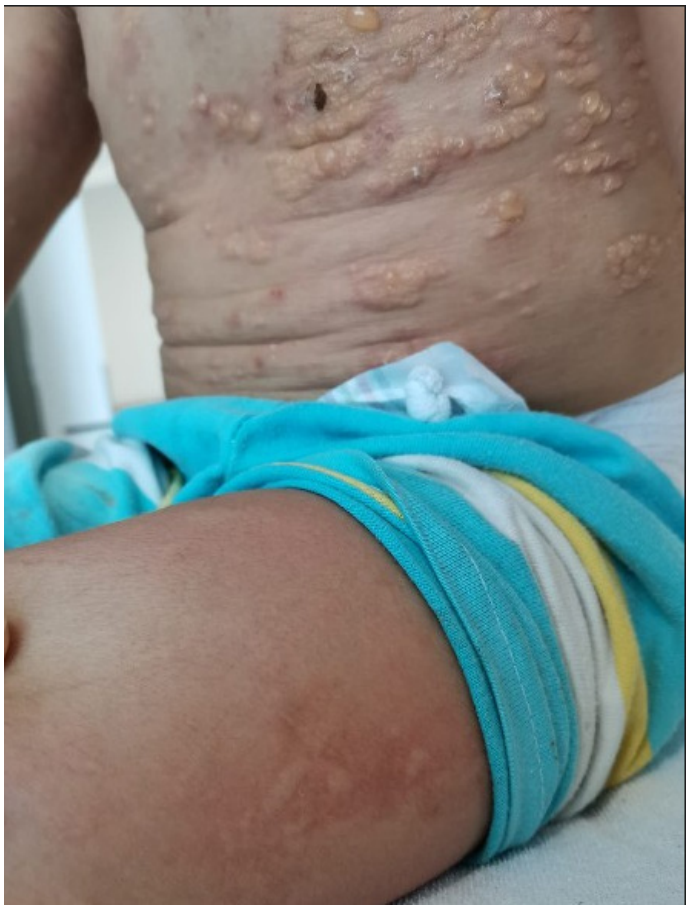
In 1878, Sangester first time called this disease urticaria pigmentosa (UP) to define dermal lesions (2), while the term 'CM' was first introduced in 1936 by Sezary and Chauvillon (3). Cutaneous mastocytosis is a relatively frequent condition in pediatric dermatology clinics. Sagher and Even-Paz found that its prevalence ranged from 1: 1.000 to 1: 8.000 dermatology patients in the USA (4), whereas Torrelo et al. report 5.4 cases per 1.000 pediatric dermatology cases in Spain (5) and it was noted to be 1: 500 first-time pediatric dermatology cases (6).

Figure I. Maculo-papular cutaneous mastocytosis in one of our patients



The WHO divides CM into three main categories: Maculopapular cutaneous mastocytosis (MPCM), diffuse cutaneous mastocytosis (DCM), and solitary skin mastocytoma (Figure 1 and 2). If CM contains ≤3 lesions are named mastocytomas whereas MPCM is between 4 and 100 dermal lesions. The DCM category involves diffuse cutaneous involvement (7-10).

Figure II. Diffuse cutaneous mastocytosis appearance in one of our patients



Review of different clinical features in case series of CM in literature

Incidence of various clinical presentations in childhood CM reported being different in the literature. The largest assessment of CM included 1,747 cases over 54 years. While the most common symptom was pruritus seen in 48% of the cases, blistering was described in a third of the pediatric patients, flushing in 25%, digestive symptoms in 20%, and anaphylaxis in 5% (9,11). Isolated pulmonary symptoms e.g., rhinorrhea or bronchospasm due to MC mediators are infrequently seen in CM (9,12,13). Another retrospective series had 71 cases of CM, 53 with UP, 12 mastocytomas, and 6 DCM; 94% of the cases manifested with positive Darier's sign, 92% had an onset in the first year of childhood, and 80% better or had natural resolution of disease in time (6). The most common skin lesion was macules, subsequently plaques or papules, and bullae in 16 cases. Accompanying symptoms and signs were lacking in mastocytoma cases excluding itching; diarrhea was present in 7 out of 36 UP cases and

2 of 5 DCM (12).

Among 65% of UP cases, 20% presented at birth and 80% during the first year of life in a retrospective review of 180 patients with CM. Of the 117 cases of UP, 13 were familial and only one generation was affected in 5 affected families. No familial history was reported in mastocytoma cases. Of the mastocytoma cases, 75% and 56% of UP cases had full resolution of the lesions over a 1-15-year follow-up period. Associated symptoms in UP cases involved asthma in 10.3%, flushing in 12.8%, fever in 1.7%, and abdominal pain in 2% (14).

Triggers of Mast Cell Activation

Triggers MC activation include certain foods, cold water, hot baths, exercise, heat, venoms, rubbing of cutaneous lesions, alcohol, nonsteroidal anti-inflammatory drugs (NSAIDs), polymyxin B, narcotics, anticholinergics and some general anesthetic drugs (table 1). When exposed to certain triggers, MC release mediators such as histamine, eicosanoids, prostaglandins, leukotrienes, heparin, proteases, and certain cytokines causing the symptoms of mastocytosis (7,15). Different histamine-containing nutrients, including treated meats, smoked fish, ripened cheeses, fermented foods, eggplant, and spinach, and histamine-releasing nutrients such as citrus fruits, strawberries, pineapple, tomatoes, nuts, shellfish, chocolate, and additives are thought to be triggers (8).

Treatment Prophylactic treatment

General measures include avoidance of any triggers, such as sudden temperature changes, and rubbing of lesions (table 1). The triggering factors need to be taught to patients and parents, such as heat, cold, sudden changes in temperature, moisture, stroking of skin lesions, sleep deprivation, exercise, emotional stress, spicy food, and febrile illnesses (14,15). Additionally, parents should recognize the drugs that can result in MC activation including morphine, codeine, vancomycin, aspirin, ketorolac, and muscle relaxant drugs (16).

Surgical treatment

In certain patients, if Darier's sign can be generated simply and physical exposure is unavoidable daily encounters, concealing the cutaneous lesion with an adhesive bandage or shielding dress can be of help (15). Surgical removal only ought to be debated in very unusual conditions, e.g. irritable solitary mastocytomas in a critical site or for the risk of induction of anaphylaxis in profoundly penetrated mastocytoma (16).

Table I. Triggers of mast cell activation

Environmental	
Sudden temperature changes	Heat, cold, moisture
Pressure	
Friction/rubbing/ stroking	
Sunlight	
Allergens	Venom, pollen, molds, mite, food, etc.
Human Body	
Exercise	
Teething	
Fever	
Infections	
Endoscopy (GIS operation)	
Sleep deprivation	
Emotions	Stress, Anxiety
Drugs	
Analgesics (NSAIDs)	Aspirin, ketorolac
Opioid/narcotics	Morphine, codeine
Systemic anesthetics	
Muscle relaxants	Atracurium, mivacurium, vecuronium, pancuronium, cisatracurium
Polymyxin B	
Anticholinergics	
Radiocontrast media	
Antibiotics	Vancomycin
Vaccinations	
Cough suppressants	
IFN- α 2b	
Dietary	
Alcohol	
Caffeine	Chocolate
Spices	
Fermented food	Aged cheeses
Cured meats	
Smoked fish	
Bacterial toxins	
Additives	
Food containing histamine	Eggplant, spinach
Histamine-releasing foods	Citrus fruits, nuts, shellfish, strawberries, pineapple, tomatoes

Management during operation

The risk of perioperative anaphylaxis in children with CM even with widespread dermal participation and high serum tryptase levels is low. The most pronounced nonspecific histamine-releasing drugs, opiates and neuromuscular blocking agents/muscle relaxants such as atracurium and mivacurium should be avoided if possible or administered slowly. On the other hand vecuronium, pancuronium, cisatracurium and fentanyl and related agents have not been reported to cause significant perioperative reactions. In the perioperative period, it is essential to have adrenaline

and isoflurane available (7). Postoperatively, with care, we can select paracetamol (17). Intradermal skin testing of drugs utilized in general anesthesia and muscle-relaxing agents should be considered preoperatively. Patterson protocol could be used for procedures involving intravenous contrast due to the increased risk of anaphylaxis and other reactions due to anesthesia (7). The risk can be diminished using a supplementary intravenous premedication of H1-/H2-antihistamines 1-2 hr (or clemastine 0.05 mg/kg orally divided q8-12hr) and prednisone 12-24 h/1-2 hr prior operation (bolus 2 mg/kg and then 1 mg/kg; respectively), and/or sedatives as required on the operation day (7,9). Before the surgical intervention, decreasing anxiety or even preoperative sedation (oral diazepam) can be recommended (table 2).

Table II. Therapeutic options for cutaneous mastocytosis

Therapeutic options	
Prophylactic treatment	The triggering factors need to be taught to patients and parents
Surgical treatment	Concealing the cutaneous lesion, surgical removal
Management during operation	Keep adrenaline and isoflurane available, use paracetamol instead of NSAIDs, Intradermal skin testing of drugs and Patterson protocol if necessary
General management in CM	Oral H1 and/or H2 antihistamines, anti-leukotriene (montelukast), oral disodium cromoglycate, PUVA
Topical treatment	Topical corticosteroid, pimecrolimus, tacrolimus, disodium cromoglycate (1- 4%)
Self-injectable epinephrine	Adrenaline autoinjector
Biologicals	Omalizumab and Nemolizumab

PUVA: methoxy psoralen treatment with long-wave ultraviolet A radiation; CM: cutaneous mastocytosis; NSAID: nonsteroidal anti-inflammatory drugs.

General management in CM

Oral H1 and/or H2 antihistamines help control the itching and flushing in UP. Prophylactic oral non-sedating antihistamines, e.g. cetirizine, in children who have not yet demonstrated any symptoms can be recommended. In patients with persistent symptoms, H2 antihistamine or anti-leukotriene (montelukast) can be added to the treatment schedule (9). H2 antihistamines (cimetidine, famotidine), or proton pump inhibitors, (e.g., omeprazole, pantoprazole, lansoprazole) may provide help with gastrointestinal system (GIS) symptoms including abdominal pain, cramping, and diarrhea. Oral disodium cromoglycate is also can be used for digestive symptoms (15-20 mg/kg/d divided into 3 doses) (9).

Severe CM types, e.g. diffuse bullous disease, or life-threatening MC-mediator release types can profit from oral methoxy psoralen treatment with long-wave ultraviolet A radiation (PUVA). Although phototherapy with ultraviolet A (UVA)1 light, narrowband UVB, or PUVA treatment can heal the cutaneous lesion, it should only be utilized in certain patients with possible carcinogenic risk in mind in generally self-healing pediatric CM. PUVA is most helpful in non-hyperpigmented diffuse bullous disease while the response is typically weak in nodular or plaque types (9,12).

Topical treatment

In solitary mastocytomas, the local utilization of a strong topical glucocorticosteroid can be useful by reducing itching and improving cosmetic issues in cases with recurrent pruritus. Mild or medium potent glucocorticosteroids are better in infants; mometasone furoate 0.1% cream can be considered in a newborn with DCM. High potent glucocorticosteroids such as clobetasol propionate 0.05% may be used for solitary mastocytoma therapy (16). Systemic corticosteroid efficiency has been seen in a few cases of severe skin disease. However, adverse effects on the dermis such as atrophy and adrenocortical suppression are limiting factors in their long-term use (table 2).

Topical pimecrolimus with excellent results and its safety profile is recommended instead of corticosteroids in pediatric CM. Calcineurin inhibitors, pimecrolimus, and tacrolimus were shown to decline the density of murine dermal MCs and histamine synthesis by tempting MC apoptosis. Furthermore, pimecrolimus has a noteworthy anti-inflammatory effect by preventing T-cell stimulation, hindering inflammatory cytokine production, and immunomodulatory effects with a weak systemic immunosuppressive potency (15,16). Topical treatment with 1% pimecrolimus cream utilized twice daily on MPCM and mastocytoma lesions in 18 children with CM with a mean duration of 8.3 months, some of the lesions have regressed, and even a few vanished. Clinical assessment 12 months after the completion of treatment, no recurrence of the cutaneous lesions that had resolved was observed (18). Disodium cromoglycate at 1% to 4% concentration in an aqueous solution or mixed with a water-based emollient cream may also diminish itching.

Self-injectable epinephrine (adrenaline autoinjector)

Self-injectable epinephrine in CM is suggested in children with DCM, blistering, or signs of systemic mastocytosis (SM), prior anaphylaxis attacks, and/or high baseline serum tryptase concentration (15,19).

Biologicals (Omalizumab and Nemolizumab)

A recombinant humanized monoclonal antibody that prevents the attaching of IgE to the FcεRI receptor on the surface of MCs, displayed a swift and long-term

efficiency to regulate severe MC-linked symptoms in an adolescent with recurrent anaphylaxis attacks. Studies have demonstrated that utilizing anti-IgE (omalizumab) decreases exacerbations in pediatric CM cases (15).

Since pruritus is stimulated by increased IL-31 levels and nemolizumab, a specific IL-31 antibody that is presently under development, its therapeutic utilization in severe types of CM would provide potential benefit if this drug becomes obtainable in the future (8).

Prognosis in various studies of the literature

If CM persists beyond adolescence, up to 10% of cases may advance into systemic form with a guarded prognosis (7). Among the 66 cases with CM, one developed into an indolent SM with bone marrow participation. She had skin findings of itching, wheals, and blistering from 6 months of age subsequently progressive, persistent systemic symptoms of wheezing, dizziness, and angioedema and she was diagnosed with indolent systemic mastocytosis at the age of 19 (20).

In one retrospective study where medical archives and follow-up examinations were accessible for 25 children with MPCM, with monitoring of 5 years, 76% resolved, 16% had stable disease, one had complete improvement, and one deteriorated (6). In another prospective study, 55 cases with MPCM were followed for at least 2 years, during which 9% of all cutaneous lesions had been involuted (13). In 1963, a study by Caplan et al concluded from analysis and follow-up of 112 cases that the outcome of CM patients was fatal in 2.9% (21). In a review of 67 pediatric cases, the average follow-up was 4.1 years, 36% had demonstrated resolution over 6.1 years, and 55% of the cases stayed unchanged (22). In the fifth retrospective study with a follow-up of 1- to 15 years, 35 of 62 cases with MPCM (56%) demonstrated complete regression (14). In the sixth study, 10 of 15 patients had complete improvement of the dermal disorder and symptoms at follow-up approximately of 20 years (23). In a current review of the literature, it could progress into a systemic form in around 1/100 cases with CM (15).

Conclusion

CM is confined to the skin and it occurs almost exclusively in children. CM is divided into three main categories: MPCM, DCM, and mastocytoma. Several dermatological and/or systemic pathologies should be ruled out in the differential diagnosis. All CM cases should be assessed for systemic disease development, especially in the existence of other risk factors. The prognosis of CM is superb, particularly if the CM's inception is in the first two years of life.

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