Current approach to cutaneous mastocytosis in childhood

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Abstract

Mastocytosis is a heterogeneous disorder characterized by clonal proliferation and accumulation of mast cells in one of more organs which may lead to different clinical pictures. Pathological increase and activation of mast cells in various tissues can cause different clinical pictures. Cutaneous mastocytosis limited to the skin is the most typical clinical picture observed in children and systemic mastocytosis is very rare in the pediatric age group. The diagnosis of cutaneous mastocytosis is based on clinical findings, but is often delayed due to lack of clinical awareness of the disease and lack of its consideration in the differential diagnosis. This article focuses on the current diagnosis, management and treatment of cutaneous mastocytosis in children in order to increase awareness about this issue.

(Turk Pediatri Ars 2016; 51: 123-7)

Keywords: Child, cutaneous, mastocytosis

Introduction

Mastocytosis is a disorder characterized by clonal proliferation and accumulation of mast cells in one or more organs which may lead to different clinical pictures (1). It may be in the form of cutaneous mastocytosis with involvement of the skin alone or systemic mastocytosis with involvement of multiple organs.

Mastocytosis is defined in two main ways: cutaneous mastocytosis characterized with cutaneous involvement and systemic mastocytosis characterized with involvement of the organs including liver, spleen, lymph nodes and/or bone marrow. However, a new classification was made by the World Health Organization in 2008 (Table 1) (2, 3).

Mastocytosis may be observed in all ethnic groups and age groups. In children, it is typically observed in the form of cutaneous mastocytosis and systemic mastocytosis is substantially rare (4). In adults, it is generally characterized with more serious systemic findings.

Pathogenesis

Mast cells are found in the skin and many tissues and lead to various clinical symptoms and signs by secreting many mediators when they are induced. The mediators secreted from the mast cells and their roles are shown in Table 2 (5). Abnormal accumulation of mast cells in tissues and the mediators they secrete are involved in the pathogenesis of mastocytosis. Both uncontrolled proliferation and defective apoptosis are responsible of accumulation of mast cells in tissues (6).

Mast cells originate from hematopoietic progenitor cells. Mast cell progenitors have been demonstrated in the bone marrow and peripheral blood (7, 8). It is thought that these cells migrate and differentiate and mature in various organs (9). The most important one among growth factors is "stem cell factor (SCF)". This factor is also named mast cell growth factor or KIT ligand. Mast cells develop from CD34+ progenitor cells by way of stem cell factor (10, 11). The effects of stem cell factor on mast cells and mast cell progenitors is mediated by KIT which is encoded by c-kit protooncogene

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Received: 26.01.2016

Accepted: 20.02.2016

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DOI: 10.5152/TurkPediatriArs.2016.2418

Table 1. Classification of mastocytosis (adapted from the references number 2 and 3)

1. Cutaneous mastocytosis
a) Maculopapular type (urticaria pigmentosa) (the most common type with the best prognosis)
b) Diffuse cutaneous mastocytosis
c) Solitary mastocytosis
2. Indolent (Slowly progressing) systemic mastocytosis (good prognosis)
3. Systemic mastocytosis in association with a clonal hematological non-mast cell lineage disease (variable prognosis)
4. Aggressive systemic mastocytosis (poor prognosis)
5. Mast cell leukemia (MCL) (poor prognosis)
6. Mast cell sarcoma (poor prognosis)
7. Extracutaneous mastocytosis (good prognosis-rare)

Table 2. Mediators released from the mast cells and their roles (5)

Mediator	Functions
Histamine	Bronchoconstriction, tissue edema, increased vascular permeability, collagen synthesis, fibroblast growth, epithelial cell induction
Heparin	Anticoagulant, fibroblast activation, endothelial cell migration
Triptase	Degradation of respiratory allergens, IgE binding, increased TGF- β secretion, increased heart rate, increase in constriction of smooth muscles in the respiratory tract
Chymase	Increase in mucus secretion, matrix degradation, increase in type 1 procollagen production, decrease in adhesion of T cells to respiratory muscles, IL-1 β activation
PGD2	Bronchospasm, increased tissue edema and mucus secretion, eosinophil, increase in Th2 cells and basophilic infiltration, activation of dendritic cells
LTC4/LTD4	Bronchospasm, increase in tissue edema and mucus secretion, increase in IL-13, increase in IL-4 secretion from eosinophils, mast cell induction

and is a tyrosine kinase receptor for SCF (12). Stem cell factor and SCF-related KIT activation are essential for development and differentiation of mast cells. "Activating" mutations located in the kinase region of the KIT protein lead to excessive development of mast cells and their progenitors (13). Among these mutations which lead to transformation of cells, Asp-816-Val mutation is observed commonly especially in adult patients with systemic mastocytosis (14-16).

Cutaneous mastocytosis

Cutaneous mastocytosis was reported in 1936 for the first time by Sezary and Chauvillon (17). Although there is no

clear data about the prevalence of cutaneous mastocytosis, it was reported to be 1/500 in children presenting to pediatric dermatology clinics in one study (18). It is clinically manifested as urticaria pigmentosa, diffuse cutaneous mastocytosis or solitary mastocytosis (2).

Urticaria pigmentosa is the most common form. It is generally manifested as a stable, red-brown lesions in the form of maculopapular plaque, nodule or bulla in any region of the body, scalp, face trunk and extremities in infancy (19). Pruritus of varying degrees accompanies the lesions (20). In cutaneous lesions, erythema and urticaria may develop around the lesion with physical trauma including rubbing and friction; this is called "Darier's sign" (21). Sudden blushing may develop in the lesions with hot bath, cold water or exercise (22). On histopathological examination of the cutaneous lesions, mast cell accumulation is observed along the papillary dermis and reticular dermis and inside the subcutaneous adipose tissue (23). Therefore, the incidence of atopic disease is increased compared to the general population (24).

Diffuse cutaneous mastocytosis is a rare type of mastocytosis which occurs in childhood. It is usually observed in adults. Lesions in the form of diffuse xanthogranulomas similar to yellow-orange subcutaneous nodules or diffuse red bullae are observed (19). Dermatographism mostly result in hemorrhagic bullae. Urticaria pigmentosa has a more severe course and may lead to life-threatening conditions by causing hypovolemic shock, mast cell leukemia, gastrointestinal hemorrhage and cachexy (25). Mast cell infiltration is observed around the blood vessels along the whole dermis (23).

Single or multiple brown nodules are observed in solitary mastocytoma. If these nodules are exposed to any trauma including friction, they may lead to flushing and systemic symptoms including hypotension. Histologically, mast cell infiltration which shows extensions into the papillary and reticular dermis is observed in the subcutaneous tissue without cytological atypia (23).

Diagnosis

The diagnosis of cutaneous mastocytosis is made clinically and confirmed histopathologically. On histopathological examination of the cutaneous lesions, mast cell accumulation is found and the mast cells are differentiated by metachromatic staining by Giemsa and Toluidine dyes (26). SCORMA (SCORing MASTocytosis in-

A: Body surface area involved

B: Severity

Criteria	Severity	Scoring
1. Pigmentation/erythema	()	0: absent
2. Vesicle	()	1: mild
3. Swelling	()	2: moderate
4. Positive Darier's sign	()	3: severe

C: Subjective signs

1. Triggering factors	0.....	10
2. Flushing	0.....	10
3. Diarrhea	0.....	10
4. Pruritus	0.....	10
5. Local bone pain	0.....	10

SCORMA index: $A/5 + 5B + 2C/5$

Figure 1. Mastocytosis severity scoring (adapted from the reference number 28)

Figure 2. Flowchart for the diagnosis of mastocytosis (adapted from the reference number 19)

dex) and serum triptase level should be evaluated in all pediatric patients with mastocytosis (27). The SCORMA index is a scoring system which is used in specifying the disease severity (Figure 1) (28). The flowchart which

Table 3. Diagnostic criteria for systemic mastocytosis (2)

Diagnostic criteria for systemic mastocytosis (2008)

- Major;
 1. Multifocal mast cell infiltrates in tissue sections (groups composed of more than 15 mast cells in the bone marrow and/or extracutaneous organs)
- Minor;
 1. Fusiform, immature or atypical mast cells in tissue sections or bone marrow (>25%)
 2. Detection of KIT D816 V mutation (in the bone marrow, blood or tissue)
 3. CD2 and/or CD25 expression in mast cells
 4. A persistent triptase level of >20 ng/mL (if there is no myeloid clonal disease in association)

A diagnosis of systemic mastocytosis is made in presence of 1 major and 1 minor criterion or 3 minor criteria

should be followed when there is a suspicion of mastocytosis is presented in Figure 2 (19).

Generally, bone marrow aspiration and biopsy are not recommended in children aged below 5 years with acute-onset cutaneous mastocytosis. However, it is beneficial to perform bone marrow aspiration and biopsy, if additional conditions including abnormal complete blood count, hepatosplenomegaly and lymphadenopathy are present. Bone marrow biopsy should be absolutely performed, if systemic mastocytosis is considered. Evaluation of bone marrow aspiration by way of flow-cytometry is diagnostic.

The diagnostic criteria for systemic mastocytosis specified by the World Health Organization in 2008 are presented in Table 3 (2).

Treatment

Generally, treatment is not needed in patients with isolated cutaneous mastocytosis. Patients and families should be informed that they should avoid excessively hot bath, sudden temperature changes, physical stimulation, hardly rubbing of the skin, stress, bee bite and drugs including aspirin, codeine, morphine, alcohol and radiocontrast substances containing iodide to prevent exacerbations (23). Education related with use of epinephrine autoinjector in case of sudden hypotension which is observed as a result of acute degranulation of mast cells should be given. In this case, corticosteroid and antihistaminic treatment may be administered additionally.

In children aged above 2 years, topical therapies may be given, if cosmetic problems are present. Closed dressing may be preferred, if the lesions cover 10% of the body. However, topical corticosteroid creams should be preferred, if the lesions cover more than 10% of the body (29). One should be cautious in terms of secondary bacterial infections while using these creams. If pruritus, erythema and swelling occur, systemic H1 and H2 antihistaminics and cromolyn sodium may be helpful (29).

Treatment is controversial in diffuse cutaneous mastocytosis. If frequent hospitalization is required or life-threatening reactions are observed, imatinib treatment may be tried. Imatinib mesilate is a type 2 kinase inhibitor. It induces cell growth and apoptosis by binding to adenosine 3 phosphate and the adjacent kinase domain. It may lead to cardiomyopathy and stunted growth in children. Other side effects include nausea, vomiting, diarrhea, increased liver enzymes, hypophosphatemia, edema, rash, granulocytopenia, anemia and thrombocytopenia. However, these side effects are observed rarely in children. The initial dose in children is 200 mg/m²/day. One should taper the dose to the dose which is sufficient to control the cutaneous lesions as soon as possible. Complete blood count, liver enzyme tests and growth rate should be absolutely checked (25).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Z.T., D.Ö.; Design - Z.T., D.Ö.; Supervision - Z.T., D.Ö.; Funding - Z.T., D.Ö.; Materials - Z.T., D.Ö.; Data Collection and/or Processing - Z.T., D.Ö.; Analysis and/or Interpretation - Z.T., D.Ö.; Literature Review - Z.T., D.Ö.; Writing - Z.T., D.Ö.; Critical Review - Z.T., D.Ö.; Other - Z.T., D.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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