TÜBİTAK

Turkish Journal of Medical Sciences

http://journals.tubitak.gov.tr/medical/

Research Article

Turk J Med Sci
(2014) 44: 504-510
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doi:10.3906/sag-1303-36

Comparison of cutaneous mastocytosis with onset in children and adults*

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Received: 06.03.2013 • **Accepted:** 08.07.2013 • **Published Online:** 31.03.2014 • **Printed:** 30.04.2014

Background/aim: Mastocytosis is a heterogeneous group of diseases characterized by the abnormal infiltration of mast cells in the skin and sometimes other organs. This study aimed to compare the demographic, clinical, and histopathological findings of cutaneous mastocytosis with onset in children and in adults.

Materials and methods: Patients diagnosed with cutaneous mastocytosis in 2 different dermatology clinics between 2007 and 2011 were included in the study. Demographic characteristics of the patients as well as localization and type of the cutaneous lesions, presence of symptoms, Darier's sign, family history, systemic involvement, and histopathological evaluations were retrospectively examined.

Results: Out of the 30 cases of cutaneous mastocytosis, 60% of patients were male (n = 18) and 40% were female (n = 12). Twenty-two patients had childhood-onset mastocytosis (≤15 years) and 8 patients had adult-onset mastocytosis. The onset of the disease occurred before the age of 2 years in all cases of childhood onset. Patients with adult-onset mastocytosis had statistically significantly more systemic involvement than those with childhood-onset mastocytosis ($P < 0.05$).

Conclusion: Cutaneous mastocytosis is a benign disease in children without systemic involvement and is usually sporadic.

Key words: Cutaneous mastocytosis, children, adult

1. Introduction

Mastocytosis is a heterogeneous group of diseases and occurs as a result of abnormal proliferation of mast cells involving the bone marrow, liver, spleen, lymph nodes, gastrointestinal system, and skin. All clinical types of mastocytosis are rarely seen. The most commonly involved organ is the skin (1,2). Based on the World Health Organization classification, cutaneous mastocytosis (CM) is divided into 3 groups: maculopapular type CM (MPCM), which was previously named urticaria pigmentosa according to traditional classification; diffuse CM (DCM), and solitary CM (SM). MPCM also has special forms including plaque form, nodular form, and telangiectasia macularis eruptiva perstans (TMEP) (3,4). Mastocytosis can be classified as being of childhood onset (less than 15 years old) and adult onset (more than 15 years old) based on its clinical appearance and course (5). In this study, we compared demographic features, clinical, and histopathological findings of childhood- and adult-onset of CM.

2. Materials and methods

We retrospectively evaluated 30 patients that were clinically and histopathologically diagnosed with CM in 2 different dermatology clinics between April 2007 and August 2011. Patients' age, sex, age of onset of CM, clinical types of CM, clinical symptoms, distributions of lesions, presence of Darier's sign, family history, systemic involvement, histopathological findings, treatments, and follow-up findings were obtained from the charts. For an assessment of systemic involvement, total cell count, liver function test, kidney function test, bone X-ray, abdominal ultrasonography, and bone marrow biopsy (in adult patients) were performed. A phone interview was conducted with the patients to obtain more information on clinical courses. Data analysis was performed with SPSS 15.0. The Mann–Whitney U test was used for categorical variability relationship analysis. A P-value of less than 0.05 was considered statistically significant.

* This work was presented as a poster at the 24th National Dermatology Congress, 9–13 October 2012, in Gaziantep, Turkey.

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3. Results

Of these 30 patients, 22 (73.3%) were in the childhood group and 8 (26.7%) were in the adult group. Sixty percent of the patients (n = 18) were male and 40% of them (n = 12) were female. The male-to-female ratio was 1:0.6.

In the childhood group, 12 (54.5%) were male and 10 (45.5%) were female. The mean age was 2.4 ± 2.1 years (ranging from 7 months to 9 years). The age of onset of disease was 5.8 ± 4.5 months (ranging from 1 month to 18 months). The male-to-female ratio was 1:0.8. In the adult group, 6 patients were male (75%) and 2 were female (25%). The mean age was 33 ± 7 years (ranging from 19 years to 41 years). The male-to-female ratio was 1:0.3.

In the childhood group, all patients developed their first lesion before the age of 2 years. Seventy-seven percent of the patients (17 cases) developed the lesions within 6 months following birth. None had a lesion at birth. The distribution of childhood patients according to age of onset of the lesions is summarized in Figure 1. In the adult group, the mean of age of lesion onset was 30 ± 7 years (ranging from 17 years to 39 years). Distribution of adult patients according to lesion onset age is shown in Figure 2.

In the childhood group, 19 patients had MPCM (Figure 3) and 3 patients had SM (Figure 4). Of the symptoms, 72.7% (15 patients) of the patients developed itching. In the adult group, 7 patients had MPCM (87.5%) and 1 patient (12.5%) had TMEP. Itching was the most common symptom (7 patients; 87.5%) in the adult group. The difference in the incidence of itching between the 2 groups was not statistically significant (P > 0.05). Other symptoms, including flushing, headache, fatigue, abdominal pain, nausea, vomiting, and diarrhea, were not detected in either group.

In the childhood group, the most common types of lesions were macular (n = 8) and maculopapular (n = 7). Bullous lesions developed in 2 cases (1 case: SM; 1 case: MPCM). The most commonly involved areas were the trunk (n = 6) and the upper and lower limbs (n = 4). Three childhood patients with MPCM developed facial involvement, as well. Three childhood patients with SM only developed trunk involvement. The most common types of lesions in the adult group were maculopapular lesions (n = 5) followed by macular lesions (n = 3). The most commonly involved area was the trunk plus upper and lower limbs (n = 5) and only the trunk (n = 2) in the adult group. No facial or neck involvement was detected in the adult group. There was no statistically significant difference in the lesions' morphology and locations between the 2 groups (P > 0.05). The involved areas in the childhood and adult groups are shown in Figure 5.

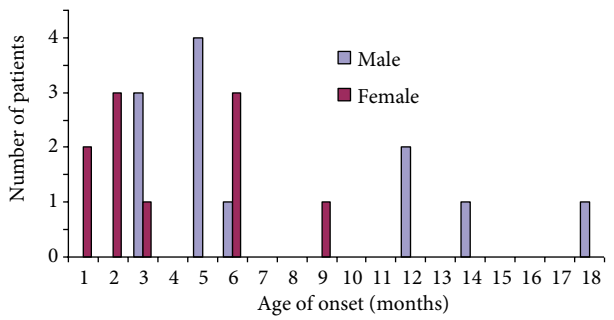

Figure 1. Age distribution of childhood-onset mastocytosis.

Figure 2. Age distribution of adult-onset mastocytosis.

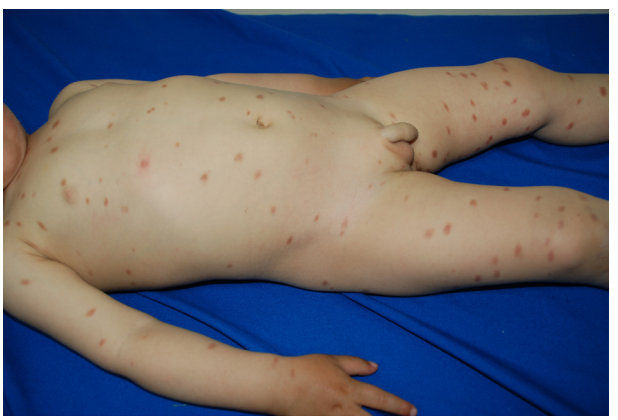

Figure 3. Maculopapular cutaneous mastocytosis. Diffuse red-brown macula and papules on the trunk and extremities.

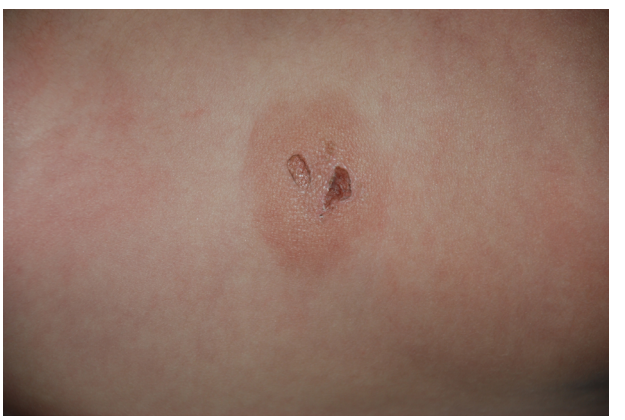

Figure 4. Solitary mastocytoma. Erythematous plaque with eroded vesicles on the trunk.

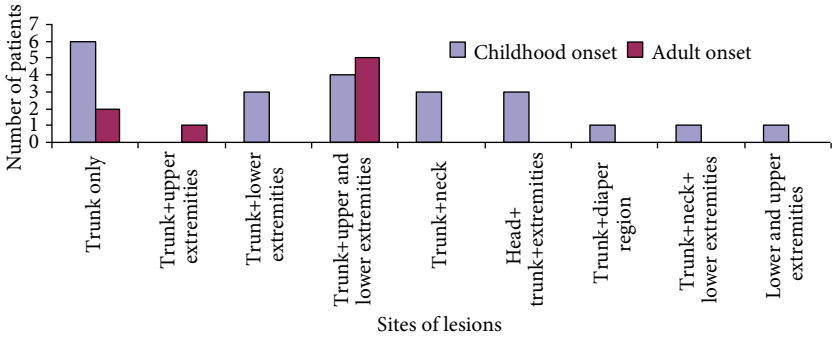

Figure 5. Distribution of lesion sites in childhood- and adult-onset mastocytosis.

Darier's sign was positive in 19 patients (86.4%) in the childhood group. Three patients with negative Darier's sign had MPCM. All patients with SM had positive Darier's sign. Darier's sign was positive in 75% of the adult group. The 2 adult patients with negative Darier's sign had TMEP and MPCM clinical types. There was no statistically significant difference in the incidence of positivity of Darier's sign between the 2 groups ($P > 0.05$).

No family history was present in the childhood or adult patients. The systemic involvement work-up was negative in the childhood group. Bone marrow biopsy showed systemic involvement in 2 adult patients with CM. Systemic involvement was statistically significantly higher in the adult group than the childhood group ($P < 0.05$). The skin biopsy from the childhood and adult patients with CM showed mast cell infiltration without cellular atypia around the blood vessels and dermis (Figure 6a). Metachromatic granules in the mast cells were detected with Toluidine blue staining (Figure 6b). An intense cytoplasmic staining with C-kit (CD117) of mast cells was obtained with immunohistochemical staining (Figure 6c).

The patients were treated with mast cell stabilizers such as H1 and H2 antihistamines, ketotifen, cromolyn sodium, and low- and moderate-potency topical steroids. Two adult patients (TMEP and MPCM) were also treated with narrow-band ultraviolet B. Of the 2 patients with systemic involvement, 1 was treated with interferon and the other was closely monitored without any additional treatment. However, most of the patients did not come back for follow-up visits regularly. Three childhood patients were reached over the phone. The lesions were completely resolved in 2 of the patients (1 case of MPCM, 1 case of SM) and the lesions were partially resolved with no new lesions in 1 of the patients (MPCM). Two adult patients treated with phototherapy stopped treatment at the end of first and second month of the treatment, respectively. There was no change in their lesions. Demographic and clinical features of the adult and childhood patients are shown in the Table.

4. Discussion

Mastocytosis is a rare disease most commonly seen in infants and children. The incidence of the disease shows variability between studies (1/200–8000) (6,7). One of the studies from Turkey performed by Seraslan et al. detected a high prevalence rate 1:234 (8).

In our study, 73.3% of the patients had childhood onset of the disease. This rate was 64% in Middelkamp et al.'s study including adult- and childhood-onset CM cases (5). In our study, the male/female ratio was 1:0.8 in the childhood group and 1:0.3 in the adult group. Although the frequency of disease was higher in males, it was not statistically significant. Our findings were consistent with the previous results in which the male/female ratio was 1.5–1.8/1 (5,6,9). However, the female frequency was higher in other studies (male/female ratio of 1/1.5–1.8) (8,10).

Skin lesions usually occur at early ages in cutaneous mastocytosis. In Middelkamp et al.'s study, 50% of the lesions started before the age of 2, 14% of them between 2 and 15 years, and 36% in adult years (5). In the study by Akoglu et al., the lesions started during the first 6 months of life and 78.2% of lesions started before 13 months. In addition, no congenital clinical type was detected in these studies (10). In our study, 73.3% of lesions started before age of 2. The rest of the lesions (26.7%) started after the age of 17. The peak incidence in the childhood group was the age of 1 and the percentage of lesion onset during the first 6 months of age was 77%. No congenital form was detected. Our findings were consistent with previous results.

The clinical types of cutaneous mastocytosis are MPCM, DCM, and SM. The special forms of MPCM include the plaque form, nodular form, and TMEP (3,4). The frequency of subtypes shows differences in different studies. Previous studies reported that 80%–85.7% of patients developed MPCM and 20%–21.4% of them had SM (8,10). In our study, the frequency of MPCM was 86.4% and that of SM was 13.6% in the childhood group. TMEP was not detected in the childhood group.

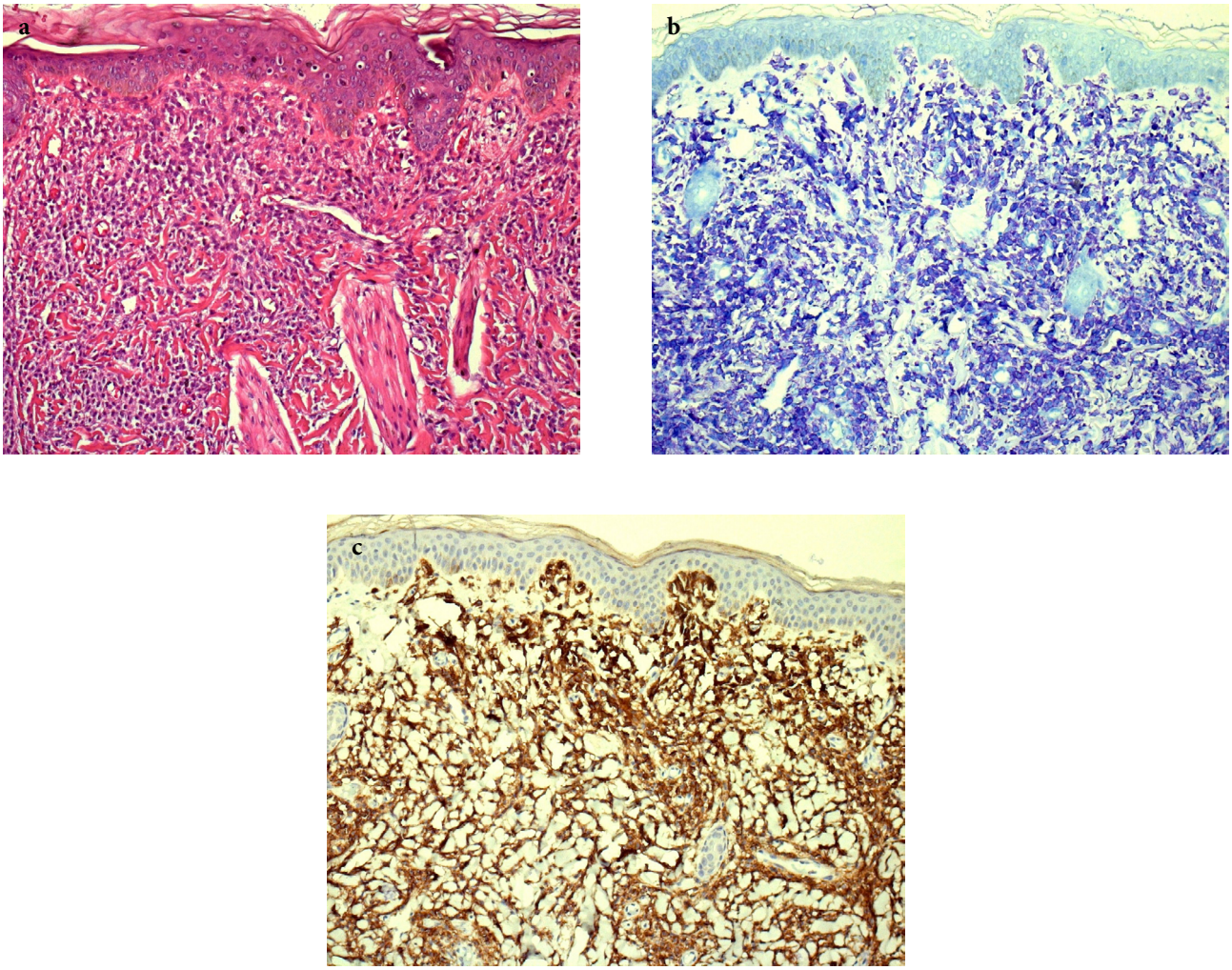

Figure 6. Staining of samples. a) Intense mast cell infiltration in the dermis (H&E, 200×). b) Metachromatic staining of the mast cells with toluidine blue in the dermis (200×). c) Intense positive staining with CD117 (immunoperoxidase, 200×).

The frequency of MPCM was 87.5% in the adult group. One patient with TMEP (12.5%) was detected in the adult group. The most frequently seen clinical type was MPCM in our study. The skin lesions can be red or brown papules, plaque, or nodules. MPCM usually does not involve the palmoplantar region, face, and scalp (2,11,12). However, 3 patients with MPCM developed facial involvement in our study. There was no significant difference in the frequency of clinical types in the childhood and adult groups. In our study, 3 patients (13.6%) had SM in the childhood group. These SM lesions that were located on the trunk were consistent with the literature. Diffuse CM is a rare and severe form of CM (1,13). There was no DCM case in our study. We only detected 1 case of TMEP in the adult group.

Family history is rare in mastocytosis. Around 50 family cases have been reported, but typical genetic penetrance has not been described (14–18). There was no family history in our study.

Itching, flushing, headache, vertigo, fatigue, and gastrointestinal symptoms including abdominal pain, nausea, vomiting, and diarrhea can be seen in mastocytosis. The symptoms can result in the release of mast cell mediators, particularly histamines (5,8). Middelkamp et al. found symptoms including itching, flushing, abdominal pain, diarrhea, and headache in 50% of childhood patients and 61% of adult patients (5). In our study, itching was detected in 72.7% of the childhood group and 87.5% of the adult group. There was no significant difference in the frequency of itching between the 2 groups ($P > 0.05$).

Darier's sign is an erythematous and urticarial flare surrounding the lesions that occurs as a result of mast cell degranulation and inflammatory mediator release induced by minor trauma (14). Serarslan et al. found Darier's sign positivity in 92.9% of patients and Akoglu et al. detected Darier's sign positivity in 89.5% of patients (8,10). In our study, we found Darier's sign positivity in 86.4% of

Table. Demographic and clinical data of the patients with cutaneous mastocytosis.

	Childhood-onset mastocytosis (n = 22)	(%)	Adult-onset mastocytosis (n = 8)	(%)
Female	10	45.5	2	25
Male	12	54.5	6	75
Age	2.4 ± 2.1 years (7 months to 9 years)		33 ± 7 years (19–41 years)	
Age of onset	0.5 ± 0.4 (1–18 months)		30 ± 7 (17–39 years)	
Cutaneous form				
MPCM	19	86.4	7	87.5
TMEP	–	–	1	12.5
DCM	–	–	–	–
SM	3	13.6	–	–
Type of lesions				
Macule	8	36.4	3	37.5
Macule-papule	7	31.8	5	62.5
Papule	3	13.6	–	–
Plaque	3	13.6	–	–
Bulla	2	9	–	–
Nodule	1	4.5	–	–
Symptoms				
None	6	27.3	1	12.5
Pruritus	15	72.7	7	87.5
Family history	–	–	–	–
Darier's sign				
Positive	19	86.4	6	75
Negative	3	13.6	2	25
Systemic involvement	–	–	2	25

MPCM: Maculopapular cutaneous mastocytosis, TMEP: telangiectasia macularis eruptiva perstans, DCM: diffuse cutaneous mastocytosis, SM: solitary cutaneous mastocytosis.

the childhood patients and 75% of the adult patients; the difference between these groups was not statistically significant ($P > 0.05$).

The histopathological examination of cutaneous mastocytosis showed intense mast cell infiltration in the dermis and around blood vessels. In MPCM, mast cells usually distribute scatteredly around blood vessels. In SM, mast cells usually cluster around blood vessels and occasionally in the subcutaneous tissue. Mast cell infiltration can be shown by hematoxylin and eosin staining. Giemsa stain and toluidine blue can be used to stain metachromatic granules in mast cells. Histochemical staining such as chloroacetate esterase or immunohistochemical stain such as C-kit (CD117) can be used for further investigations (8,14).

Cutaneous mastocytosis usually recovers spontaneously and rarely needs to be treated. The first treatment step is to avoid triggering factors that can cause mast cell mediator release. Medical treatments include H1 and H2 antihistamines, mast cell stabilizers such as ketotifen and cromolyn sodium, topical corticosteroids, PUVA, and narrow band UVB therapy (2,3,14,19). In our study, H1 antihistamines, mast cell stabilizers, and topical steroids were administered in the childhood cases and phototherapy was applied in 2 adult cases. The treatment options for systemic involvement are chemotherapy and interferon alpha (20). In our study, systemic involvement was detected in 2 (25%) adult patients. One was treated with interferon therapy and the other was followed without any treatment.

There is a remarkable difference in terms of systemic involvement and prognosis between childhood and adult patients. Systemic changes are usually rare, transient, and benign in childhood patients. In contrast to the childhood patients, bone marrow disease, bone alterations, and

gastrointestinal involvement are frequently seen in adult patients and they usually show a progressive and chronic course (6,21). In our study, systemic involvement was not seen in the childhood patients and was only seen in 2 adult patients.

In children, mastocytosis usually spontaneously recovers by puberty (22). Our patients did not come to follow-ups regularly. We reached the childhood patients over the phone. Of 3 childhood patients, the skin lesions were completely resolved in 2 patients (1 case of MPCM, 1 case of SM) and the lesions were diminished without any new lesions in 1 patient with MPCM. Two of our patients with adult onset CM (25%) developed systemic involvement. Skin lesions were not detected in these 2 patients during the treatment course. These 2 adult patients were reached over the phone and did not develop any new lesions.

The evaluation of systemic involvement can be done by the measurements of serum tryptase levels; a level above 20 ng/mL is a minor criterion of systemic mastocytosis (7). The level of serum tryptase is important in diagnosis and in clinical follow-up (7,23,24). Serum tryptase is usually negative in patients with CM and is high in patients with systemic mastocytosis (1). Increased levels of mast cells derived from prostaglandin D2, heparin levels, and increased serum and urine levels of N-methylhistamine and n-methylimidazole acetic acid can be seen in patients with systemic involvement (14). In our study, we could not retrospectively assess serum tryptase, heparin, or urine histamine metabolites levels in our patients.

In conclusion, our results from childhood- and adult-onset CM patients were consistent with previous results. Mastocytosis is a rare disease. The cutaneous form of mastocytosis usually has a benign course, but systemic involvement can be life-threatening. Childhood-onset mastocytosis has a better prognosis than adult-onset mastocytosis. Mastocytosis-related systemic involvement is more common in adult-onset mastocytosis. Diagnosis is usually made based on clinical findings. Further studies involving a large number of patients with this rare disease should be performed to develop new treatment approaches for mastocytosis.

References

1. Briley LD, Phillips CM. Cutaneous mastocytosis: a review focusing on the pediatric population. Clin Pediatr (Phila) 2008; 47: 757–761.
2. Heide R, Beishuizen A, De Groot H, Den Hollander JC, Van Doormaal JJ, De Monchy JG, Pasmans SG, Van Gysel D, Oranje AP; Dutch National Mastocytosis Work Group. Mastocytosis in children: a protocol for management. Pediatr Dermatol 2008; 25: 493–500.
3. Kutlubay Z, Yardımcı G, Engin B, Tüzün Y. Cutaneous mastocytosis. J Turk Acad Dermatol 2011; 5: 1153r1.
4. Amon U, Hartmann K, Horny HP, Nowak A. Mastocytosis—an update. J Dtsch Dermatol Ges 2010; 8: 695–711.
5. 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: 115–120.
6. 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: 285–290.
7. Lange M, Niedoszytko M, Renke J, Gleń J, Nedoszytko B. Clinical aspects of paediatric mastocytosis: a review of 101 cases. J Eur Acad Dermatol Venereol 2013; 27: 97–102.
8. Serarslan G, Atik E, Canda Ş. Pediatric cutaneous mastocytosis: demographic, clinical and histopathological findings. Turk J Dermatol 2008; 2: 69–72 (article in Turkish with an abstract in English).
9. Ben-Amitai D, Metzker A, Cohen HA. Pediatric cutaneous mastocytosis: a review of 180 patients. Isr Med Assoc J 2005; 7: 320–322.
10. Akoglu G, Erkin G, Cakir B, Boztepe G, Sahin S, Karaduman A, Atakan N, Akan T, Kolemen F. Cutaneous mastocytosis: demographic aspects and clinical features of 55 patients. J Eur Acad Dermatol Venereol 2006; 20: 969–973.
11. Kanwar AJ, Sandhu K. Cutaneous mastocytosis in children: an Indian experience. Pediatr Dermatol 2005; 22: 87–89.
12. Hannaford R, Rogers M. Presentation of cutaneous mastocytosis in 173 children. Aust J Dermatol 2001; 42: 15–21.
13. Wolff K, Komar M, Petzelbauer P. Clinical and histopathological aspects of cutaneous mastocytosis. Leuk Res 2001; 25: 519–528.
14. Calka O. Urticaria pigmentosa. In: Tüzün Y, Gürer MA, Serdaroğlu S, Oğuz O, Aksungur VL, editors. Dermatoloji. 3rd ed. İstanbul, Turkey: Nobel Tıp Kitabevleri; 2008. pp. 2005–2010 (in Turkish).
15. Rosbotham JL, Malik NM, Syrris P, Jeffery S, Bedlow A, Gharraie S, Murday VA, Holden CA, Carter ND. Lack of c-kit mutation in familial urticaria pigmentosa. Br J Dermatol 1999; 140: 849–852.
16. Fowler JF Jr, Parsley WM, Cotter PG. Familial urticaria pigmentosa. Arch Dermatol 1986; 122: 80–81.
17. Oku T, Hashizurne H, Yokote R, Sano T, Yamada M. The familial occurrence of bullous mastocytosis (diffuse cutaneous mastocytosis). Arch Dermatol 1990; 126: 1478–1484.
18. Anstey A, Lowe DG, Kirby JD, Horton MA. Familial mastocytosis: a clinical, immunophenotypic, light and electron microscopic study. Br J Dermatol 1991; 125: 583–587.

19. Prignano F, Troiano M, Lotti T. Cutaneous mastocytosis: successful treatment with narrowband ultraviolet B phototherapy. Clin Exp Dermatol 2010; 35: 914–915.

20. Lange M, Nedoszytko B, Górska A, Zawrocki A, Sobjanek M, Kozlowski D. Mastocytosis in children and adults: clinical disease heterogeneity. Arch Med Sci 2012; 8: 533–541.

21. Ben-Amitai D, Metzter A. Pediatric mastocytosis. Ann Dermatol Venereol 1998; 125: 196.

22. Lanternier F, Cohen-Akenine A, Palmerini F, Feger F, Yang Y, Zermati Y, Barète S, Sans B, Baude C, Ghez D et al. Phenotypic and genotypic characteristics of mastocytosis according to the age of onset. PLoS One 2008; 3: e1906.

23. Valent P. Diagnostic evaluation and classification of mastocytosis. Immunol Allergy Clin North Am 2006; 26: 515–534.

24. Pardanani A, Akin C, Valent P. Pathogenesis, clinical features, and treatment advances in mastocytosis. Best Pract Res Clin Haematol 2006; 19: 595–615.