

ORIGINAL ARTICLE

Diffuse cutaneous mastocytosis: analysis of 10 cases and a brief review of the literature

M. Lange,^{†,*} M. Niedozytko,[‡] B. Niedozytko,[†] J. Łata,[‡] M. Trzeciak,[†] W. Biernat[§]

[†]Department of Dermatology, Venereology and Allergology, Medical University of Gdansk, Gdansk, Poland

[‡]Department of Allergology, Medical University of Gdansk, Gdansk, Poland

[§]Department of Pathology, Medical University of Gdansk, Gdansk, Poland

*Correspondence: M. Lange. E-mail: m.lange@gumed.edu.pl

Abstract

Background Diffuse cutaneous mastocytosis (DCM) is an extremely rare disease characterized by mast cell (MCs) infiltration of the entire skin. Little is known about the natural course of DCM.

Objectives We decided to characterize clinical manifestations, the frequency of MCs mediator-related symptoms and anaphylaxis, risk of systemic mastocytosis (SM) and prognosis, based on 10 cases of DCM, the largest series published to date.

Methods Diffuse cutaneous mastocytosis, DCM was confirmed by histopathological examination of skin samples in all cases. SCORing Mastocytosis (SCORMA) Index was used to assess the intensity of DCM. The analysis of clinical symptoms and laboratory tests, including serum tryptase levels was performed. Bone marrow biopsy was done only in selected cases.

Results Large haemorrhagic bullous variant of DCM (five cases) and infiltrative small vesicular variant (five cases) were identified. The skin symptoms appeared in age-dependent manner; blistering predominated in infancy, whereas grain-leather appearance of the skin and pseudoxanthomatous presentation developed with time. SM was not recognized in any of the patients. Mast cell mediator-related symptoms were present in all cases. Anaphylactic shock occurred in three patients. Follow-up performed in seven cases revealed slight improvement of skin symptoms, reflected by decrease of SCORMA Index in all of them. Serum tryptase levels declined with time in six cases.

Conclusions Diffuse cutaneous mastocytosis, DCM is a heterogeneous, severe, cutaneous disease, associated with mediator-related symptoms and risk of anaphylactic shock. Although our results suggest generally favourable prognosis, the review of the literature indicate that SM may occur. Therefore, more guarded prognosis should be given in DCM patients.

Received: 22 May 2011; Accepted: 27 October 2011

Conflict of interest

None declared.

Funding sources

The study was supported by the grant of the Polish Ministry of Science and Higher Education NN 402424939.

Introduction

Mastocytosis is a heterogeneous group of myeloproliferative disorders characterized by pathological increase and accumulation of mast cells (MCs) in one or more organs, affecting particularly the skin (cutaneous mastocytosis, CM), bone marrow, liver, spleen and the lymph nodes (systemic mastocytosis, SM).^{1–4} The activating mutation of *KIT* gene in exon 17 (D816V) is found in most of SM patients.^{1–5} In contrast to adult-onset mastocytosis, childhood-onset mastocytosis is usually skin disease characterized by

benign and self-limiting course.^{6–9} Paediatric mastocytosis has been considered a reactive disorder and it remains unclear whether or not the condition is clonal.^{8,10}

According to WHO recommendations the major criterion of SM is histological demonstration of multifocal compact MCs infiltrates in the extracutaneous tissues. Minor criteria are: (i) more than 25% of MCs in extracutaneous infiltrates are spindle-shaped or atypical; (ii) detection of the *KIT* point mutation at codon 816; (iii) expression of CD2 and/or CD25 by MCs in extracutaneous organs; and (iv) serum tryptase level exceeding 20 ng/mL. To

establish the diagnosis of SM one major and one minor criterion or three minor criteria should be present.^{1,2,11}

Diffuse cutaneous mastocytosis, DCM is an extremely rare and the most severe clinical presentation of CM, characterized by entire skin infiltration of MCs.^{12–14} Cutaneous symptoms consist of widespread spontaneous blistering with erosions, erythroderma or thickening of the skin.^{9,14} Due to the widespread and heavy MC load in the entire skin DCM is often associated with severe mast cell mediator-related symptoms such as: flushing, itching, blistering, diarrhoea, abdominal pain, vomiting, hypotension, headache and anaphylactic shock.^{12–14} Rubbing of skin lesions invokes release of mast cell mediators and results in the reddening and urticarial swelling. This response is known as the Darier's sign and is considered diagnostic for all forms of CM.^{8,9,12}

Owing to low incidence of DCM, little is known about its natural course, the frequency of systemic involvement and anaphylaxis in this disease. Therefore, we described the clinical features of 10 patients with DCM, the evolution of skin presentation, and frequency and severity of symptoms dependent on the release of MC mediators. We also tried to assess the risk of systemic involvement in patients who initially presented with DCM. To the best of our knowledge, it remains the largest series of cases with this uncommon form of mastocytosis published to date.

Patients and methods

A total of 150 children and 130 adults were registered in the Gdansk Center with various clinical forms of mastocytosis between January 2002 and March 2011. The Gdansk Mastocytosis Center is a reference site for the whole Polish population of mastocytosis patients. DCM was revealed in 10 of 280 patients with mastocytosis. The study is a clinical analysis of nine DCM children and one adult patient with childhood-onset DCM. The diagnosis of mastocytosis and assignment to the disease category was made according to the WHO criteria and classification. DCM was recognized in patients with the entire skin involvement. In all the cases the medical history, physical examination, histopathological examination of the skin lesions [including Giemsa staining and c-kit (CD117) immunostaining], serum tryptase levels, a complete blood cell count with peripheral smear, serum levels of transaminases, alkaline phosphatase and abdomen ultrasound were performed. Bone marrow biopsy, flow cytometric patterns and genetic examination of *KIT* mutation at codon 816 were done in the adult patient. Bone marrow biopsy was also performed in two children with tryptase levels over 100 ng/mL and/or organomegaly. D816V mutation was analysed in bone marrow using ASA PCR method. Flow cytometric examination of bone marrow consisted of CD2 and CD25 staining. Total serum tryptase levels were determined in all cases by a commercial fluorescent enzyme immunoassay (UniCAP assay and UniCAP 100 instrument; Phadia, Sweden). To assess the extent and activity of skin lesions, SCORMA Index was applied.^{15,16} The SCORMA Index is a clinical scoring system based on a semi-quantitative analysis of the extent (A), the intensity (B)

and subjective complains (C) for the patients with cutaneous mastocytosis. The SCORMA Index formula is $A/5 + 5B + 2C/5$, and it ranges from 5.2 to 100.

Patients were followed in 6 month-long periods. The same diagnostic procedures and histopathological examination were performed on presentation and on follow-up.

Informed consent for publication of data and clinical photographs were obtained from the adult patient and from the parents of children enrolled into the study. The study was approved by the local ethics committee.

Results

Diffuse cutaneous mastocytosis, DCM was diagnosed in 10 patients (3.57% of all mastocytosis cases in our centre). The study group consisted of nine children aged from 4 months to 11 years and one adult patient with onset of DCM at the age of 3 months who was verified to our centre after 22 years of disease duration. The onset of the disease occurred before or at the age of 6 months in eight cases and was congenital in two cases. Clinical characteristics of the study group was presented in Tables 1 and 2.

Correct initial diagnosis of CM was rendered in four children, whereas the diagnoses varied in the remaining ones (see Table 1). The final diagnosis of DCM was established in the Dermatology Department and the Allergology Department of Gdansk Medical University where the diagnostic procedures have been completed. Bullous lesions were the most common first presentation of the disease which was found in seven cases. Blistering appeared in all patients during infancy and occurred periodically up to 2–4 years of age. Large haemorrhagic bullous variant (Fig. 1) and infiltrative small vesicular variant (Fig. 2) were found in equal proportions of children (see Table 1). Pseudoxanthomatous manifestation developed in an adult male patient with childhood-onset DCM. In this case the earliest skin lesions appeared in 3 months of life and manifested as extensive erythematous plaques with periodical blistering on the trunk and the face which are typical for infiltrative small vesicular variant. During the first year of life, skin lesions gradually evolved into diffuse erythema followed by thickening of the entire skin with reddish-brown colour and grain-leather appearance in childhood. Numerous nodular infiltrative lesions resembling xanthomas appeared after puberty (Fig. 3). Histologically, the skin was diffusely and densely infiltrated by mature MCs. The infiltrate spared the epidermis. The diagnosis based on routine staining was confirmed by CD117 immunohistochemistry (Fig. 4a–d). In six patients (no. 1, 2, 3, 4, 6, 10) erythroderma and blistering present in infancy evolved into thickening of the entire skin, with a reddish-brown or yellow-brown colour and grain-leather appearance. Positive Darier's sign, severe dermatographism and diffuse infiltration of the skin appeared in all patients on presentation and during follow-up.

Systemic alterations in a study group are presented in Table 2. Ultrasound imaging showed hepatomegaly in two cases. However,

Table 1 Cutaneous manifestation of diffuse cutaneous mastocytosis (DCM)

Patient	Gender	Age of onset	First symptom	MB%*	BC**	Initial diagnosis	Darier's sign	Variant of DCM
1	M	At birth	Bullae	30	3 years	SSSS	Yes	Large bullous
2	F	3 months	Bullae	25	4 years	CM	Yes	Infiltrative small vesicular
3	M	6 months	Bullae	30	3 years	EBA	Yes	Large bullous
4	F	4 months	Bullae	40	3 years	IB	Yes	Large bullous
5	M	3 months	Erythema	20	1 year	CM	Yes	Infiltrative small vesicular
6	F	6 months	Bullae	10	2 years	CM	Yes	Infiltrative small vesicular
7	M	2 months	Erythema	25	2 years	CM	Yes	Large bullous
8	F	3 months	Bullae	25	2 years	IB	Yes	Large bullous
9	F	At birth	Bullae	15	Ongoing	IB	Yes	Infiltrative small vesicular
10	M	3 months	Erythema	20	2 years	AD	Yes	Infiltrative small vesicular

MB%* – percentage of the skin involved at maximal blistering.

BC** – the age at which blistering ceased.

SSSS, staphylococcal scalded skin syndrome; CM, cutaneous mastocytosis;

EBA, epidermolysis bullosa acquisita; IB, impetigo bullosa; AD, atopic dermatitis.

Table 2 Clinical characteristics of 10 diffuse cutaneous mastocytosis cases

Patient	Age at V1	Monitoring period	Tryptase			SCORMA index			Organomegaly	Bone marrow biopsy	Treatment
			V1 ng/mL	VL ng/mL	EI %	V1	VL	EI %			
1	3 years	8 years, ongoing	22	17	22.7	82	62	24.4	H	Normal	H1, H2, GCS
2	13 months	4 years, ongoing	103	54	47.5	89	82	7.9	H, L	Normal	H1, H2, GCS
3	17 months	5 years, ongoing	106	33	68.8	87	70	19.5	No	ND	H1, H2 GCS
4	11 years	Discontinuation	2.7	ND	–	89	ND	–	No	ND	H1, H2 GCS
5	15 months	2 years, ongoing	23	20	13	82	69	15.8	No	ND	H1, H2
6	11 months	4 years, ongoing	29.7	22.4	24.6	87	76	12.6	No	ND	H1, H2
7	2 years	5 months, ongoing	28	ND	–	82	ND	–	No	ND	H1, H2
8	18 months	2 year, ongoing	9.4	8	14.9	80	76	5	No	ND	H1, H2
9	4 months	3 month, ongoing	16.6	ND	–	90	ND	–	No	ND	H1, H2 GCS
10	22 years	1 year	12.4	17.8	Elevation	87	82	5.7	No	Normal	H1, H2 GCS

V1 – first visit/VL – last visit in the Department of Dermatology, Medical University of Gdansk.

**Figure 1** Large haemorrhagic bullous variant of diffuse cutaneous mastocytosis.

it was not associated with elevation of liver function parameters and occurred transiently in the monitoring period. Lymphadenopathy was found on physical examination in one case and it

resolved spontaneously with time. There were no clinically significant abnormalities on peripheral blood analysis and serum biochemistry in any of the patients. Trephine bone marrow biopsy was performed in three cases and did not disclose any pathological findings. In children, trephine biopsy was performed only if systemic involvement was highly suspected (two cases), whereas in the adult DCM patient it was a standard procedure. Bone marrow biopsy was performed in children with tryptase level exceeding 100 ng/mL and/or organomegaly. Bone marrow biopsy was also indicated in child no. 3 with tryptase level of 106 ng/mL, but it was refused by his parents. Serum tryptase levels in this child decreased gradually with time and amounted to 33 ng/mL at the age of 6 years and no other clinical symptoms were suggestive of SM in this case. In the adult DCM patient, flow cytometry of bone marrow did not disclose CD2- and CD25-positive MCs, D816V KIT mutation in the bone marrow MCs was not identified and



Figure 2 Infiltrative small vesicular variant of diffuse cutaneous mastocytosis.

serum tryptase levels were under 20 ng/mL. He did not show any SM criteria. Finally, SM has not been diagnosed in any of patients under study.

Mast cell mediator-related symptoms were reported in all patients as demonstrated in Table 3. Chronic itching was the most



Figure 3 Pseudoxanthomatous manifestation of diffuse cutaneous mastocytosis in an adult male.

common symptom present in all cases followed by periodic flushing, hypotension, headache and diarrhoea. Mediator-related symptoms occurred as bouts in five of our DCM patients. They were characterized by simultaneous occurrence of pruritus, flushing, blistering, hypotension, vomiting and diarrhoea and were reported only in children below 2–3 years of age. Anaphylactic shock occurred in three DCM cases. Patient No.1 had three such events;

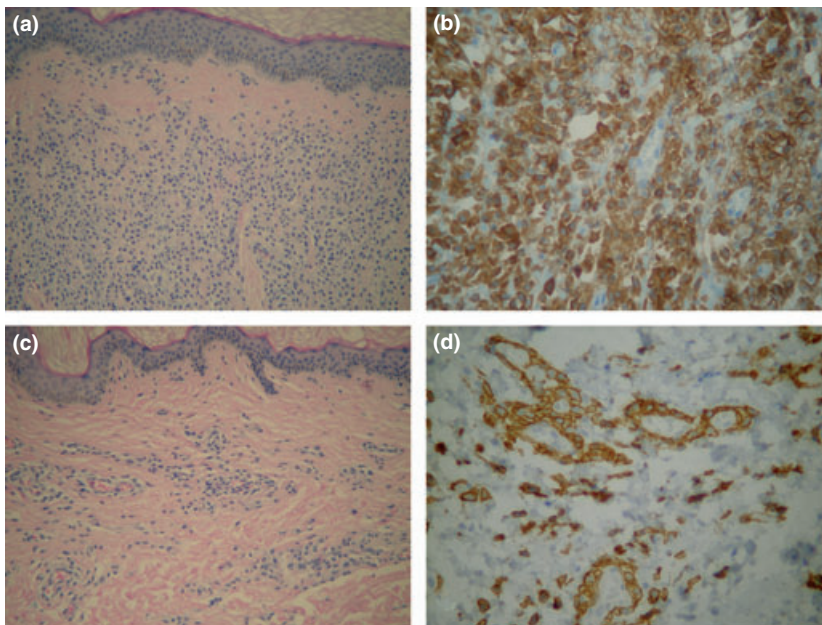


Figure 4 The histological appearance of the grossly involved (a,b) and uninvolved (c,d) skin in a patient with diffuse cutaneous mastocytosis. The diffuse dense infiltrate of mature mast cells in the dermis sparing the epidermis (a) confirmed by CD117 immunohistochemistry (b). The seemingly uninvolved skin contains perivascular infiltrate composed exclusively of mast cells (c). Angiocentricity of mast cell infiltrates demonstrated by CD117 staining (d).

Table 3 Mast cell mediator-related symptoms in diffuse cutaneous mastocytosis patients

Patient	Flushing	Itching	Diarrhoea	Headache	Hypotension	Bouts	Anaphylactic shock
1	Yes	Yes	Yes	Yes	Yes	Yes	Yes, 3 episodes
2	Yes	Yes	Yes	Yes	Yes	Yes	Yes, 1 episode
3	Yes	Yes	No	Yes	Yes	Yes	No
4	Yes	Yes	Yes	Yes	Yes	Yes	Yes, 2 episodes
5	Yes	Yes	No	No	No	No	No
6	Yes	Yes	No	No	No	No	No
7	Yes	Yes	No	No	No	No	No
8	Yes	Yes	No	No	No	No	No
9	No	Yes	No	No	No	No	No
10	No	Yes	No	No	Yes	Yes	No
Total	8	10	3	4	5	5	3

Bout – simultaneous occurrence of flushing, blistering, hypotension, vomiting, diarrhoea in children under 2–3 years of age.

they were induced by application of ketamin, clindamycin and MRI-contrast medium. Anaphylactic reaction to ketamin was also identified in patient no. 2, whereas in patient no. 4 the provoking factor was not revealed.

Seven patients had been followed for a period of 1–8 years with a frequency of one visit every 6 months (see Table 2). During follow-up period complete remission of skin symptoms was not observed in any of the patients. However, partial improvement of the skin lesions and the general patient performance was found in all monitored cases. SCORMA Index decreased (5–24.4%) with time in these patients, nevertheless it remained high. Decrease in tryptase levels was reported in six cases and it was particularly remarkable in those with initial high serum tryptase levels.

Discussion

Results of our study indicate that DCM is an uncommon, clinically heterogeneous disease associated with potentially life-threatening mediator-related symptoms in a considerable number of patients. Two clinical variants of DCM described in the literature were found in children of this study, i.e., large haemorrhagic bullous and infiltrative small vesicular.¹⁴ Moreover, we observed that the skin symptoms appeared in age-dependent manner. Extensive bullous lesions predominated in infancy, whereas diffuse infiltration of the skin developed further in the course of the disease as it has been previously reported.^{9,17}

The limitation of the study is relatively small number of DCM patients due to extremely rare incidence of the entity. However, our analysis remains the largest series published to date. To the best of our knowledge we managed to include all Polish patients with DCM, because Gdansk center is the referral site for mastocytosis patients in our country. DCM amounted to 3.57% of all mastocytosis cases recorded in our files. It corresponds to the frequency reported in the large paediatric studies, which ranged from 0.6% to 8% and these values confirm that DCM remains a rare form of CM.^{6,9,18,19}

The onset of DCM has usually been reported within the first 6 months of life or at birth and this was compatible with our

observations.^{7,9,12} The occurrence of extensive bullous lesions, which is regarded as a typical feature of infantile DCM, appeared as the first or the predominant symptom of this condition in the majority of our patients.^{12–14} In six cases incorrect initial diagnosis of staphylococcal scalded skin syndrome (SSSS), epidermolysis bullosa acquisita, impetigo bullosa and atopic dermatitis was established. These findings indicate that the initial diagnosis of infantile DCM is difficult. There are at least two reasons for this: lack of maculo-papular or plaque lesions, which are characteristic for childhood CM and rarity of DCM refraining paediatricians and dermatologists from inclusion of this entity into differential diagnosis. Moreover, the presence of extensive bullae may suggest an infectious, congenital or autoimmune bullous disease. DCM cases mimicking SSSS or erythema multiforme have been reported in the past.^{20–22} Nevertheless positive Darier's sign and the presence of mediator-related symptoms are highly suggestive of mastocytosis, which should be confirmed by histopathological examination.²³

Two clinical presentations of DCM have been described in infants: large haemorrhagic bullous variant and infiltrative small vesicular variant.¹⁴ The disease may present with various clinical features in children, teenagers and adults. Pseudoxanthomatous lesions, DCM with large, tumour-like mastocytomas and pachydermia with extensive skin folding have been reported.^{9,14,24–30} In our series, blistering variants were found in infants and small children whereas pseudoxanthomatous skin lesions developed after puberty in the patient who initially presented with infantile small vesicular form of DCM. The evolution of the clinical presentation was observed in all our cases during follow-up. Blistering, which predominated in children under the age of two, ceased with time and grain-leather texture of the skin with nodular infiltrates appeared. In teenagers and adults, the skin becomes less reactive. However, diffuse hyperpigmentation, with leather-like appearance usually persists.^{9,12–14} We used the SCORMA Index to evaluate severity of DCM on presentation and during follow-up, as this method provides the standardized information on the extent and activity of CM and imposes no burden on the patient, which is particularly

important in children.²³ The SCORMA Index is comparable with that used for atopic dermatitis (SCORAD) and psoriasis (PASI); its clinical applications have been published.^{15,16} In our series SCORMA Index was high on presentation. Decrease of the index during follow-up ranging from 5% to 24.4% reflects only slight improvement although treatment with blockers of H1 and H2 receptors was applied in all cases. These findings strongly indicate that DCM is the form of CM with low propensity for regression.

The infiltration of the entire skin by MCs in DCM predispose to release of large quantities of mediators evoking general symptoms with high risk of the most severe anaphylactic reactions.^{12,31–33} Triggering factors for MCs degranulation are mechanical irritation of the skin, heat, insect bites, particularly hymenoptera venom, radiocontrast media, opioids and drugs used in general anaesthesia.^{4,32,33} Similar to our observations, itching, flushing, diarrhoea and hypotension are the most frequently reported symptoms.^{3,7,9,12} The incidence of anaphylactic shock in DCM is difficult to estimate because a rarity of the entity causes that the majority of cases is described as case reports.^{31,34,35} Heide *et al.* did not identify any life-threatening events in their eight DCM patients in contrast to three of 10 of our patients who experienced this complication.¹⁴ It is noteworthy that sudden death in infants with bullous mastocytosis due to shock or gastrointestinal haemorrhage has already been reported.^{35,36}

Little is known about frequency of SM in patients who initially presented with DCM. In the large study of 173 cases of paediatric mastocytosis, Hannaford *et al.* reported only three cases of DCM with further systemic dissemination occurring in two of them.⁹ Numerous case reports indicate that DCM may present with more severe complications and increased risk of SM development.^{29,37–40} MC infiltration of the liver, spleen, lymph nodes and bone marrow, chronic diarrhoea, malnutrition, myeloproliferative disorders and *KIT* mutation have been described in children with DCM.^{29,37–40} Taking these reports into consideration with our observation of significant frequency of anaphylaxis in DCM we recommend more thorough diagnosis including multidisciplinary consultations and careful monitoring of the disease course. We share the opinion presented by Heide *et al.* that bone marrow analysis in DCM children should be performed only if systemic involvement is highly suspected.¹⁴

Evaluation of serum tryptase level appears a useful tool to monitor DCM patients, because it closely correlates with the disease course and is considered a surrogate marker of the disease severity.^{1,16,41} In our series, tryptase levels were exceeding 20 ng/mL in six children and in two of them the levels were more than 100 ng/mL, although the condition was limited to the skin. Initially high tryptase levels in infants declined with time in all monitored cases. Our findings indicate that serum tryptase levels can be very high in the first 2 years of life, but they mostly decline after the age of two. It has been recommended to perform bone marrow investigation in children with suspected haematological disease, serum tryptase persistently exceeding 100 ng/mL or rising

and when other signs of SM appear.^{3,23} Results of our study suggest that tryptase levels may reflect an intensity of cutaneous involvement. In our DCM cases highly elevated tryptase levels, particularly in the early stage of the disease, correlated with significant extent and severity of cutaneous lesions and mediator-related symptoms. Temporal decline in tryptase levels was associated with decrease of the intensity of these symptoms and the risk of life-threatening events. Serum tryptase level has been proposed an indicator of the total body MC burden.^{41,42} This may explain elevation of serum tryptase levels in DCM cases which are characterized by MC infiltration of the entire skin.

Both our findings and published data concerning the course of DCM indicate that the disease is especially dangerous in the first 2 years of life because of the risk of life-threatening events as well as due to extensive blistering, which gradually ceases with time. The review of the literature suggests that prognosis in DCM is uncertain. Some authors point out that if bullous eruptions manifest as the first symptom of the disease in children, the disease is more prone to progress to SM than those patients who originally presented with infiltrative lesions.^{7,43} Our observations do not support this sequential evolution of DCM and suggest rather favourable prognosis. Of particular interest is the adult patient with DCM who remains under observation for 22 years and did not show any SM criteria. None of our patients progressed into SM and this corresponds to the results reported by Heide *et al.* and Kiszewski *et al.*^{14,19} Therapeutic considerations are out of the scope of this article because discussion on it and the protocol for management has been recently published.^{22,44–47} Nevertheless, we would like to mention that in our case treatment was restricted to long-term administration of antihistamine agents. Only severe mediator-related symptoms and extensive blistering were treated periodically with oral steroids. Anaphylactic shock required steroids and adrenalin application.

In conclusion, although CM in children is generally a benign disease with favourable prognosis, diagnosis of DCM in these patients should be followed by more guarded prognosis. The authors' personal experience in the clinical care of mastocytosis patients and the review of the literature suggest that DCM cases are at risk of systemic involvement and potentially life-threatening events such as anaphylaxis, cardiovascular collapse and haemorrhage which may occur upon massive MCs mediator release. Therefore, we recommend avoiding potentially triggering factors and providing patients with an emergency set.^{1–4,23} The follow-up including organ function tests, peripheral blood analysis and the determination of serum tryptase levels is essential to rule out SM, haematological disease or other complications and to apply appropriate management.

References

- 1 Arock M, Valent P. Pathogenesis, classification and treatment of mastocytosis: state of the art in 2010 and future perspectives. *Expert Rev Hematol* 2010; 3: 497–516.

- 2 Pardanani A, Akin C, Valent P. Pathogenesis, clinical features, and treatment advances in mastocytosis. *Best Pract Res Clin Haematol* 2006; **19**: 595–615.
- 3 Valent P, Akin C, Escribano L *et al*. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007; **37**: 435–453.
- 4 Escribano L, Akin C, Castells M *et al*. Mastocytosis: current concepts in diagnosis and treatment. *Ann Hematol* 2002; **81**: 677–690.
- 5 Orfao A, Garcia-Montero AC, Sanchez L, Escribano L. Recent advances in understanding of mastocytosis: the role of KIT mutations. *Br J Haematol* 2007; **138**: 12–30.
- 6 Middelkamp Hup MA, Heide R, Tank B *et al*. Comparison of mastocytosis with onset in children and adults. *J Eur Acad Dermatol Venereol* 2002; **16**: 115–120.
- 7 Hartman K, Metcalfe DD. Paediatric mastocytosis. *Hematol Oncol Clin North Am* 2000; **14**: 625–640.
- 8 Hartman K, Henz BM. Mastocytosis: recent advances in defining the disease. *Br J Dermatol* 2001; **144**: 682–695.
- 9 Hannaford R, Rogers M. Presentation of cutaneous mastocytosis in 173 children. *Australas J Dermatol* 2001; **42**: 15–21.
- 10 Bodemar Ch, Hermine O, Palmerini F *et al*. Paediatric Mastocytosis is a clonal Disease associated with D816V and other activating c-KIT mutations. *J Invest Dermatol* 2010; **130**: 804–815.
- 11 Valent P, Horny HP, Li CY *et al*. Mastocytosis (mast cell disease): World Health Organization (WHO) classification of tumors, pathology and genetics. In Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. *Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, IARC Press, 2001: 291–302.
- 12 Wolff K, Komar M, Petzelbauer P. Clinical and histopathological aspects of cutaneous mastocytosis. *Leuk Res* 2001; **25**: 519–528.
- 13 Hartmann K, Henz BM. Cutaneous mastocytosis – clinical heterogeneity. *Int Arch Allergy Immunol* 2002; **127**: 143–146.
- 14 Heide R, Zuidema E, Beishuizen A *et al*. Clinical aspects of diffuse cutaneous mastocytosis in children: two variants. *Dermatol* 2009; **219**: 309–315.
- 15 Heide R, Middelkamp Hup MA, Mulder PG *et al*. Clinical scoring of cutaneous mastocytosis. *Acta Derm Venereol* 2001; **81**: 273–276.
- 16 Heide R, van Dorn K, Mulder PG *et al*. Serum tryptase and SCORMA (SCORing MAstocytosis) Index as disease severity parameters in childhood and adult cutaneous mastocytosis. *Clin Exp Dermatol* 2008; **34**: 462–468.
- 17 Jain R, Dogra S, Verma S *et al*. Diffuse cutaneous mastocytosis: pseudoxanthomatous variant. *J Dermatol* 2002; **29**: 354–356.
- 18 Ben-Amitai D, Metzker A, Cohen HA. Paediatric cutaneous mastocytosis; a review of 180 patients. *Isr Med Assoc J* 2005; **7**: 320–322.
- 19 Kiszewski AE, Duran-Mckinster C, Orozco-Covarrubias L *et al*. Cutaneous mastocytosis in children: a clinical analysis of 71 cases. *J Eur Acad Dermatol Venereol* 2004; **18**: 285–290.
- 20 Oranje AP, Soekanto W, Sukardi A *et al*. Diffuse cutaneous mastocytosis mimicking staphylococcal scalded skin syndrome: report of three cases. *Pediatr Dermatol* 1991; **8**: 147–151.
- 21 Golitz LE, Weston WL, Lane AT. Bullous mastocytosis: diffuse mastocytosis with extensive blisters mimicking scaled skin syndrome or erythema multiforme. *Pediatr Dermatol* 1984; **1**: 288–294.
- 22 Has C, Misery L, David L, Cambazard F. Recurring staphylococcal scalded skin syndrome-like bullous mastocytosis; the unity of cytodiagnosis and the rapid regression with steroids. *Pediatr Dermatol* 2002; **19**: 220–223.
- 23 Heide R, Beishuizen A, de Groot H *et al*. Mastocytosis in children: a protocol for management. *Pediatr Dermatol* 2008; **25**: 493–500.
- 24 Willemze R, Ruiter DJ, Scheffer E, Van Vloten WA. Diffuse cutaneous mastocytosis with multiple cutaneous mastocytomas. *Br J Dermatol* 1980; **102**: 601–607.
- 25 Walker T, von Komorowski G, Scheurlen W *et al*. Neonatal mastocytosis with pachydermic bullous skin without c-kit 816 mutation. *Dermatology* 2006; **212**: 70–72.
- 26 Avshalumov K, Pichardo R, Jorizzo JL *et al*. Bullous mastocytosis: report of a patient and a brief review of the literature. *Am J Dermatopathol* 2008; **30**: 455–457.
- 27 Srivastava N, Chand S, Singh S. Pseudoxanthomatous mastocytosis. *Int J Dermatol* 2008; **47**: 50–51.
- 28 Husak R, Blume-Peytavi U, Perommer C *et al*. Nodular and bullous cutaneous mastocytosis of the Xanthelasmoid type: case report. *Br J Dermatol* 2001; **144**: 355–358.
- 29 Caksen H, Ciftci A, Alper M. A child with systemic mastocytosis who had a facial appearance resembling an aged man. *Pediatr Dermatol* 2002; **2**: 184–185.
- 30 Sanchez-Salas MP, Lazaro AC, Martin J *et al*. Atypical pachydermatous cutaneous course of mastocytosis. *Actas Dermosifiliogr* 2007; **98**: 707–710.
- 31 Lange M, Kaszuba A. Diffuse cutaneous mastocytosis with anaphylaxis. *Adv Dermatol Allergol* 2007; **24**: 52–57.
- 32 Niedoszytko M, de Monchy J, van Doormaal JJ *et al*. Mastocytosis and insect venom allergy: safety and efficacy of venom immunotherapy. *Allergy* 2009; **64**: 1237–45.
- 33 Brockow K. Urticaria pigmentosa. *Immunol Allergy Clin N Am* 2004; **24**: 287–316.
- 34 Poterack CD, Kumudchandra JS. Shock in an infant with bullous mastocytosis. *Pediatr Dermatol* 1984; **1**: 288–94.
- 35 Murphy M, Walsh D, Drumm B, Watson R. Bullous mastocytosis: a fatal outcome. *Pediatr Dermatol* 1999; **16**: 452–5.
- 36 Simone J, Hayes W. Bullous urticaria pigmentosa with bleeding. *J Pediatr* 1971; **78**: 189–92.
- 37 Waxtein LM, Vega-Memije ME, Cortes-Franco R, Domingues-Soto L. Diffuse cutaneous mastocytosis with bone marrow infiltration in a child: a case report. *Pediatr Dermatol* 2000; **3**: 198–201.
- 38 Shah PY, Sharma V, Worobec AS *et al*. Congenital bullous mastocytosis with myeloproliferative disorder and c-kit mutation. *J Am Acad Dermatol* 1998; **39**: 119–121.
- 39 Angus J, Leach IH, Grant J, Ravenscroft JC. Systemic mastocytosis with diffuse cutaneous involvement and haematological disease presenting in utero treated unsuccessfully with vincristine. *Clin Exp Dermatol* 2007; **33**: 36–39.
- 40 Olgun N, Oren H, Oren B *et al*. Diffuse erythrodermic cutaneous mastocytosis with bone marrow infiltration. *Dermatology* 1993; **2**: 127–129.
- 41 Schwartz LB, Irani AM. Serum tryptase and the laboratory diagnosis of systemic mastocytosis. *Hematol Oncol Clin North Am* 2000; **14**: 641–657.
- 42 Brockow K, Akin C, Huber M *et al*. Levels of mast cell growth factors in plasma and suction skin blister fluid in adults with mastocytosis: correlation with dermal mast cell numbers and mast cell tryptase. *J Allergy Clin Immunol* 2002; **109**: 82–88.
- 43 Kettelhut BV, Metcalfe DD. Paediatric mastocytosis. *Ann Allergy* 1994; **73**: 197–207.
- 44 Kinsler VA, Hawk JLM, Atherton DJ. Diffuse cutaneous mastocytosis treated with psoralen photochemotherapy: case report and review of the literature. *Br J Dermatol* 2005; **152**: 179–180.
- 45 Prignano F, Troiano M, Lotti T. Cutaneous mastocytosis: successful treatment with narrowband ultraviolet B phototherapy. *Clin Exp Dermatol* 2010; **35**: 914–915.
- 46 Wolf K. Treatment of cutaneous mastocytosis. *Int Arch Immunol* 2002; **127**: 156–159.
- 47 Castells M, Metcalfe DD, Escribano L. Diagnosis and treatment of cutaneous mastocytosis in children. *Am J Clin Dermatol* 2011; **12**: 259–270.