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Characteristics and Therapeutic Strategies for Diffuse Cutaneous Mastocytosis

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IMPORTANCE Diffuse cutaneous mastocytosis (DCM) is a rare and severe subtype of pediatric mastocytosis, characterized by extensive skin involvement. Comprehensive studies on the clinical and molecular features of DCM remain limited.

OBJECTIVE To describe the clinical, molecular, and treatment-related characteristics and outcomes of a cohort of pediatric patients with a clinical presentation of DCM.

DESIGN, SETTING, AND PARTICIPANTS This retrospective study analyzed pediatric patients with a clinical presentation of DCM from January 1996 to October 2023 at Necker Children's Hospital in Paris, France.

MAIN OUTCOME AND MEASURES Data on clinical presentation, laboratory results, and *KIT* sequencing from skin biopsies and bone marrow, if available, were collected and analyzed. These data were compared with previously published findings from a pediatric cohort with maculopapular cutaneous mastocytosis (MPCM).

RESULTS The study included 33 pediatric patients, 18 (54.5%) of whom were male, with a clinical presentation of DCM, including 4 with aggressive systemic mastocytosis (ASM) and 29 with DCM. The mean (SD) age at the onset of the first clinically significant signs was 2.2 (2.2) months. A disease-revealing massive bullous eruption was noted in 9 patients (27.2%). Compared to MPCM, patients with a clinical presentation of DCM had a higher mean baseline serum tryptase level (47.5 µg/L [SD, 38.7; range, 5.0-178.0 µg/L] vs 7.4 µg/L [SD, 6.4; range, 1-45.2]; $P < .001$), a higher prevalence of anaphylaxis (4 [12.1%] vs 5 [2.4%]; $P = .02$), and a more frequent association with ASM (4 [12.1%] vs 2 [0.9%]; $P = .004$). *KIT* codon 816 variants were identified in 4 patients (19.0%), other *KIT* variants in 14 patients (66.7%), and wild-type *KIT* in 3 patients (14.3%). All 4 patients with *KIT* codon 816 variants had ASM. Seven patients (21.2%) received early systemic treatment (imatinib, midostaurin, or sirolimus depending on the type of *KIT* variants), starting at a mean (SD) age of 80.8 (135.6) months and continuing for a mean (SD) of 4.0 (2.6) years, with generally good tolerance and efficacy. Of the 15 patients without systemic treatment for more than 6 years, 13 (86.6%) exhibited spontaneous regression.

CONCLUSION AND RELEVANCE In this cohort study, DCM presentation differs significantly from MPCM, with a higher risk of anaphylaxis and aggressive systemic forms, the latter being consistently associated with the *KIT* D816V variant. Tyrosine kinase inhibitors and sirolimus were generally effective and well tolerated in this pediatric population, with the choice of treatment depending on the type of *KIT* variants.

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Supplemental content

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Mastocytosis is a rare condition characterized by the accumulation of atypical mast cells (MCs) in 1 or more tissues. Mastocytosis in children typically affects only the skin and regresses in more than 80% of patients.[1] A somatic gain-of-function variant in the *KIT* gene is observed in more than 85% of patients.[2] In children, 3 presentations of skin involvement exist: maculopapular cutaneous mastocytosis (MPCM, accounting for 75% of patients), mastocytoma (20%), and diffuse cutaneous mastocytosis (DCM) (5%), an exceptionally rare pediatric presentation in which MCs infiltrate the entire skin, unlike MPCM.[1] DCM manifestations range from skin thickening (*peau d'orange*) to erythroderma and sometimes generalized blistering caused by massive MC degranulation.[3] Overall, only case reports or small series of DCM have been published, limiting comprehensive guidance on its characteristics and treatment. The objectives of the present study were to describe clinicobiological features, disease progression, and treatment outcomes in a large cohort of patients with a clinical presentation of DCM.

Key Points

Question What are the clinical, molecular, treatment-related characteristics, and outcomes of pediatric patients with a clinical presentation of diffuse cutaneous mastocytosis (DCM)?

Findings In this cohort study of 33 pediatric patients presenting with DCM, 13 had life-threatening complications, of whom 9 presented with massive mast cell degranulation and 4 with aggressive systemic mastocytosis associated with the *KIT* D816V variant. Seven patients required cytoreductive treatment, including tyrosine kinase inhibitors and/or sirolimus, which were generally effective and tolerated well.

Meaning The clinical presentation of DCM in pediatric patients is characterized by a more severe phenotype compared to maculopapular cutaneous mastocytosis, with important implications for diagnosis and treatment, particularly in the presence of the *KIT* D816V variant.

Methods

We conducted a retrospective cohort study of a nationwide patient cohort managed at Necker Children's Hospital in Paris, France. The cohort's study protocol was approved by the local investigational review board (CPPRB Groupe Hospitalier de Paris Necker, France). All children with a clinical presentation of DCM, between January 1, 1996, and October 31, 2023, were considered for eligibility in this study (eMethods in Supplement 1).[4,5] All parents/guardians and 1 adult participant provided written informed consent. The threshold for statistical significance was $P < .05$. GraphPad, version 9.5.1 (Prism), was used for the statistical analysis.

Results

Characteristics of DCM Cohort

Thirty-three patients presenting with DCM, 18 (54.5%) of whom were male, were included in the study and had a mean age of onset of the first clinically significant signs of 2.2 (SD, 2.2; range, 0-7) months (**Table 1**). Twenty-nine patients (87.8%) had a cutaneous mastocytosis of DCM subtype, and 4 (12.1%) had aggressive systemic mastocytosis (ASM) with diffuse skin involvement clinically indistinguishable from DCM.[1] Three of the 4 patients with ASM had a form that was obvious since birth, with hepatomegaly and/or splenomegaly, as well as the presence of C-finding criteria (**Table 2**).[6] All patients exhibited cutaneous MC activation symptoms (Table 1). Four patients (12.1%) had a history of grade 3 or 4 anaphylaxis, including 1 patient whose case was complicated by multiorgan failure (patient 5; **Figure**; Table 2). The revealing signs were progressive in 24 patients (72.7%). In the cutaneous mastocytosis DCM subtype group, among the 7 patients whose DCM was revealed by massive MC degranulation and hemorrhagic bullous lesions at a median age of 1.5 months (range, 0-6 months), 2 required intensive care unit admission (Figure). In the ASM group, 2 patients experienced massive bullous MC degranulation without grade 3 or 4 anaphylaxis.

The mean baseline tryptase level was significantly higher in patients with ASM (109.8 µg/L [SD, 46.2; range, 48.6-178.0] vs 40.9 µg/L [SD, 37.8; range, 5.0-114.0]; $P < .001$). Among the 21 patients with *KIT* sequencing performed on skin biopsy and bone marrow samples (if available), 4 (19.0%, all with ASM) had a *KIT* point variant at codon 816, and 14 patients (66.7%) had a *KIT* variant in exon 8 (Table 1). None of the 8 patients tested presented with hereditary α-tryptasemia, including 2 patients with ASM and 2 patients who experienced anaphylaxis.

Comparison to MPCM Cohort

Comparing the DCM cohort (n = 33) with the previously described pediatric MPCM cohort (n = 211),[7] incident anaphylaxis was significantly more common in patients with a diffuse skin infiltration presentation than in patients with MPCM (4 of 33 [12.1%] vs 5 of 211 [2.4%], respectively; $P = .02$) (Table 1). ASM also occurred more frequently in patients with a diffuse skin infiltration (4 [12.1%] vs 2 [0.9%]; $P = .004$).

Fifteen patients without systemic treatment were followed up for more than 6 years, allowing for spontaneous regression analyses. Thirteen (86.6%) showed regression after a mean follow-up of 12.9 (SD, 4.7; range, 6.36.3-25) years. The mean (SD) time to onset of skin infiltration regression was significantly shorter in patients with DCM than in those with MPCM (45.0 [37.2] vs 105.1 [not reported] months, respectively; $P < .001$). Patients no longer developed any bullous lesions at a mean age of 34.0 (SD, 24.0; range, 3-102) months.

Nontargeted systemic treatments are listed in Table 1. Seven patients (21%) received targeted systemic treatments (tyrosine kinase [TKI] or mammalian target of rapamycin inhibitors), starting at a mean (SD) age of 80.8 (135.6) months and continuing for a mean (SD) of 4.0 (2.6) years (Table 2; eFigure in Supplement 1). Three patients with *KIT* codon 816–negative DCM received imatinib for severe degranulation episodes unresponsive to antihistamines and corticosteroids. Imatinib was effective in 2 patients and discontinued in 1 patient 2 weeks after initiation due to mild bullous flares that resolved spontaneously. Four patients received

Table 1. Clinical and Laboratory Characteristics of Patients With Diffuse Cutaneous Mastocytosis and Patients With Maculopapular Cutaneous Mastocytosis

Clinical characteristics	No. (%)				
	Clinical presentation of diffuse skin infiltration (current study) (n = 33)				
	ASM (n = 4)	DCM (n = 29)	Total (N = 33)	MPCM (n = 211)	*P* value
Sex					
Female	0	15 (51.7)	15 (45.4)	93 (44)	>.99[a]
Male	4 (100)	14 (48.3)	18 (54.5)	118 (55.9)	>.99[a]
Male to female ratio	NA	0.9	1.2	1.3	>.99[a]
Age at diagnosis, mean (SD), mo	1.3 (1.1)	16.8 (25.2)	15.1 (24.1)	42.5 (40.8)	<.001[b]
Age at onset, mean (SD; range), mo	0 (0; 0-0)	2.6 (2.2; 0-7)	2.2 (2.2; 0-7)	9.7 (30; 0-191.9)	<.001[b]
Revealing sign					
Bullous: sudden presentation characterized by extensive hemorrhagic blistering	2 (50)	7 (24.1)	9 (27.2)	NA	NA
Progressive: gradual onset of symptoms noted in clinical records	2 (50)	22 (75.9)	24 (72.7)	NA	NA
Congenital disease	4 (100)	9 (31.0)	13 (39.3)	82 (38.9)	>.99[a]
Familial mastocytosis[c]	0	2 (6.9)	2 (6.0)	22 (10.4)	.75[a]
No. of MC activation symptoms at diagnosis, mean (SD; range)	NA	NA	5.4 (2.5;1-12)	2.09 (NR)	<.001[b]
Skin	NA	NA	33 (100)	86 (40.7)	<.001[a]
Pruritus	4 (100)	26 (89.7)	30 (90.9)	NA	NA
Bullae	4 (100)	24 (82.8)	28 (84.8)	NA	NA
Flushes	4 (100)	23 (79.3)	27 (81.8)	NA	NA
Digestive tract	NA	NA	16 (48.4)	72 (34.1)	.12[a]
Abdominal pain	3 (75.0)	6 (20.7)	9 (27.2)	NA	NA
Vomiting	4 (100)	2 (6.9)	6 (18.1)	NA	NA
Diarrhea	4 (100)	7 (24.1)	11 (33.3)	NA	NA
Gastroesophageal reflux	2 (50.0)	3 (10.3)	5 (15.1)	NA	NA
Neurologic					
Sleep disorders	1 (25.0)	6 (20.7)	7 (21.2)	17 (8.0)	.03[a]
Behavioral disorder	1 (25.0)	3 (10.3)	4 (12.1)	2 (0.9)	.004[a]
Allergic reaction					
Dyspnea	0	2 (6.9)	2 (6.0)	NA	NA
Loss of consciousness	0	5 (17.2)	5 (15.1)	44 (20.8)	.64[a]
Hypotension	0	3 (10.3)	3 (9.0)	NA	NA
Anaphylaxis[d]	0	4 (13.8)	4 (12.1)	5 (2.4)	.02[a]
Absence of MC activation symptoms	0	0	0	59 (28)	.001[a]
Signs of MC skin infiltration					
Urticaria induced by physical stimulation (dermatographism/Darier-like urticaria)	4 (100)	29 (100)	33 (100)	NA	NA
Peau d'orange[e]	3 (75.0)	24 (82.8)	27 (81.8)	NA	NA
Erythroderma	1 (25.0)	5 (17.2)	6 (18.1)	NA	NA
Skin thickening	4 (100)	24 (82.8)	28 (84.8)	NA	NA
Other extracutaneous symptoms					
Hepatomegaly and/or splenomegaly[f]	4 (100)	1 (3.4)	5 (15.1)	NA	NA
Failure to thrive[g]	3 (75.0)	6 (20.7)	9 (27.2)	NA	NA
Type of mastocytosis (WHO classification)					
CM	0	29 (100)	29 (87.8)	209 (99.0)	.004[a]
ASM[h]	4 (100)	0	4 (12.1)	2 (0.9)	.004[a]
Laboratory variables					
Serum tryptase level, mean (range), µg/L	109.8 (48.6-178.0)	37.5 (5.0-114.4)	47.5 (5.0-178.0)	7.4 (1.0-45.2)	<.001[b]
Molecular sequencing of the *KIT* gene[i]	n = 4	n = 17	n = 21	n = 58[c]	NA
KIT point variant in codon 816	4 (100)	0	4 (19.0)	28 (48.3)	.02[a]
Other *KIT* variants	0	14 (82.4)	14 (66.7)	22 (37.9)	.04[a]
WT *KIT*	0	3 (17.6)	3 (14.3)	8 (13.8)	>.99[a]

(continued)

Table 1. Clinical and Laboratory Characteristics of Patients With Diffuse Cutaneous Mastocytosis and Patients With Maculopapular Cutaneous Mastocytosis (continued)

Clinical characteristics	No. (%)				
	Clinical presentation of diffuse skin infiltration (current study) (n = 33)				
	ASM (n = 4)	DCM (n = 29)	Total (N = 33)	MPCM (n = 211)	*P* value
Patients with at least 6 y of follow-up and no systemic treatment		N = 15	N = 15	N = 120	
Time to mastocytosis regression, mean (SD; range), mo	NA	45 (37.2; 9-144)	45 (37.2; 9-144)	105.1 (NR)	<.001[b]
Stabilization	NA	2 (13.3)	2 (13.3)	NA	NA
Regression[j]	NA	13 (86.6)	13 (86.6)	NA	NA
Nonsystemic treatments					
Histamine H1-receptor antagonist: desloratadine was systematically used before 1 y	4 (100)	27 (93.1)	31 (93.9)	NA	NA
Histamine H1 and H2 receptor antagonists (ranitidine, 2-4 mg/kg/d prior to 2020 or cimetidine, 10-20 mg/kg/d after 2020)[k]	3 (75.0)	20 (70.3)	23 (69.7)	NA	NA
Antileukotriene (montelukast)	1 (25.0)	9 (31.0)	10 (30.3)	NA	NA
Sodium cromoglycate, 10-40 mg/kg/d	3 (75.0)	1 (3.4)	4 (12.1)	NA	NA
Short-term corticosteroids, 0.5-1.0 mg/kg/d, for <1 mo (for bullous flares)	2 (50.0)	11 (37.9)	13 (39.4)	NA	NA
Long-term corticosteroid therapy	2 (50.0)	10 (34.5)	12 (36.4)	NA	NA
Anti-IgE drugs	0	0	0	NA	NA

Abbreviations: ASM, aggressive systemic mastocytosis; CM, cutaneous mastocytosis; DCM, diffuse cutaneous mastocytosis; IgE, immunoglobulin E; MC, mast cell; MPCM, maculopapular cutaneous mastocytosis; NA, not applicable; NR, not reported; WHO, World Health Organization; WT, wild type.

[a] Calculated with Fisher exact test.

[b] Calculated with *t* test (*z* score = −6.48).

[c] One patient has a brother with MPCM, and another has a first cousin with MPCM as well.

[d] These 4 patients did not have ASM. The cause of the anaphylaxis was a change in temperature (an elevated bath temperature) in 1 patient and was not known in the 3 other patients.

[e] *Peau d'orange* refers to a characteristic appearance of the skin that resembles the texture of an orange peel. This is caused by thickening of the dermis secondary to mast cell infiltration, leading to irregularities in texture and appearance.

[f] Hepatomegaly and/or splenomegaly were observed in 5 patients: 4 with aggressive SM (ASM) and 1 with CM. The latter patient underwent routine checkups, and a bone marrow biopsy did not show any signs of MC infiltration.

[g] Two of whom caught up with the growth curve following growth hormone treatment or treatment of the mastocytosis.

[h] All these patients presented with aggressive systemic mastocytosis, confirmed by bone marrow examination and the presence of C-finding criteria.

[i] *KIT* sequencing in this MPCM cohort was performed under the same conditions on skin samples and, if applicable, on bone marrow samples.

[j] Among the 13 patients who showed regression at the time of analysis, 7 (53.8%) had more than 50% reduction in skin involvement.

[k] Before 2020, ranitidine, 2-4 mg/kg/d, was given to patients, and after 2020, cimetidine, 10-20 mg/kg/d, was given to patients. Ranitidine was withdrawn from the market in 2020.

systemic treatment due to *KIT* D816V-positive ASM: 2 received midostaurin and 2 received sirolimus. Treatment was well tolerated and effective in 3 patients; 1 patient taking midostaurin died due to an unrelated unintentional injury. Tryptase levels decreased over time in all but 1 patient treated with midostaurin, with a mean (SD) decrease of 70.2 (94.8) µg/L (from −243.2 µg/L to 102.7 µg/L).

Literature Review of DCM

A review of the literature identified 64 case reports of patients with a clinical presentation of DCM, in which 4 of 5 patients with the *KIT* D816V variant presented with systemic mastocytosis, and 3 of them died due to severe MC infiltration (eTables 1-2 in Supplement 1).[3] Spontaneous regression was significantly more frequent in patients without the codon 816 variant compared to those with the variant (32 of 39 [82.1%] vs 1 of 9 [11.1%], respectively; $P < .001$), based on data from the 33 patients in the present cohort and the literature review (eTable 2 in Supplement 1). Patients carrying a *KIT* codon 816 variant and a diffuse skin infiltration exhibited a markedly higher risk for ASM (7 of 9 [78%] vs 0 of 39 [0%]; $P < .001$) and mortality (3 of 9 [37.5%] vs 0 of 39 [0%]; $P < .001$).

Discussion

To our knowledge, this cohort study reported the largest group of pediatric patients to date with mastocytosis and diffuse skin infiltration. Two main presenting features were observed: early, extensive bullous MC degranulation and skin infiltration with Darier-like urticaria. This sign, mimicking dermographism and present in all patients, should alert clinicians when observed in infants.

This study highlighted 2 main findings. First, anaphylaxis was more frequent in the present DCM cohort than in patients with MPCM (12.1% vs 2.4%). We recommend prescribing epinephrine autoinjectors to all patients with DCM and educating families on their use.[8] Second, children with diffuse skin involvement had a higher risk of ASM than those with MPCM (12.1% vs 0.9%), and organomegaly should raise suspicion of systemic disease.[9] Although to date, no variant has been clearly linked to poor outcomes in DCM, all patients in the present DCM cohort with diffuse skin infiltration and a *KIT* D816V variant had ASM. Based on the present DCM cohort and literature review, we propose 2 patient profiles based on *KIT*

Table 2. Patient Characteristics and Outcomes After Systemic Treatment

Patient No.	WHO classification	*KIT* variant	Bone marrow characteristics	Treatment indication	Age at treatment initiation	Treatment, starting dose per day	Duration of treatment	Type of discontinuation	Change on treatment	Pretreatment tryptase level, µg/L	Posttreatment tryptase level	Adverse events	Length of follow-up, mo
1[a]	ASM	D816V	Bone marrow smear: presence of 5% dystrophic MCs (CD25-negative, CD2-negative); D816V variant	Bone marrow dysfunction, liver function impairment, malabsorption with weight loss[b]	Child between 2 and 3 y	Sirolimus, 0.05 mg/kg	8 y (ongoing)	Tapered	Regression	187.0	87.3	None	118
2	ASM	D816V	Bone marrow biopsy: presence of dystrophic MCs (CD25-positive); D816V variant	Malabsorption with weight loss[b]	Child between 1 and 2 y	Sirolimus, 0.1 mg/kg	6 y	Tapered	Regression	114.4	32.5	None	117
3[c]	ASM	D816Y	Bone marrow smear: presence of dystrophic MCs (CD30-positive); D816Y variant	Liver function impairment[b]	Adult in their 30s	Midostaurin, 50 mg × 2/J	1 y (ongoing)	Not discontinued	Regression	178.0	89.0	None	396
4	ASM	D816V	Bone marrow biopsy: presence of 25% MCs (CD25-positive, CD30-positive); D816V variant	Bone marrow dysfunction, malabsorption with weight loss[b]	Infant <1 y	Midostaurin, 42.5 mg (10 mg/kg)	4 y	Tapered	Regression, then death[d]	93.3	196.0	None	60
5	CM	Exon 8	Bone marrow smear: normal, no MCs detected in cytologic examination and flow cytometry; *KIT* variant in exon 8	Massive bullous degranulation with organ failure	Infant <1 y	Imatinib, 20 mg (4.75 mg/kg)	4 y (ongoing)	Tapered	Regression	47.5	9.6	None	42
6	CM	Exon 8	NA[b]	Bullous flares not controlled by conventional treatment	Child between 1 and 2 y	Imatinib, 100 mg (147 mg/m^2)	5 y	Tapered	Regression	261.0	17.8	None	136
7	CM	WT	Bone marrow smear: normal, no *KIT* variant detected	Bullous flares not controlled by conventional treatment	Child approximately 1 y	Imatinib, 100 mg	2 wk	Sudden	Regression	60.0	17.0	Bullous eruption after 2 wk[e]	148

Abbreviations: ASM, aggressive systemic mastocytosis; CM, cutaneous mastocytosis; MC, mast cells; NA, not applicable; WHO, World Health Organization; WT, wild type.

[a] Patient 1 has already been described. They presented with a germline *GLI3* variant that accentuated the severity of the disease.[6]

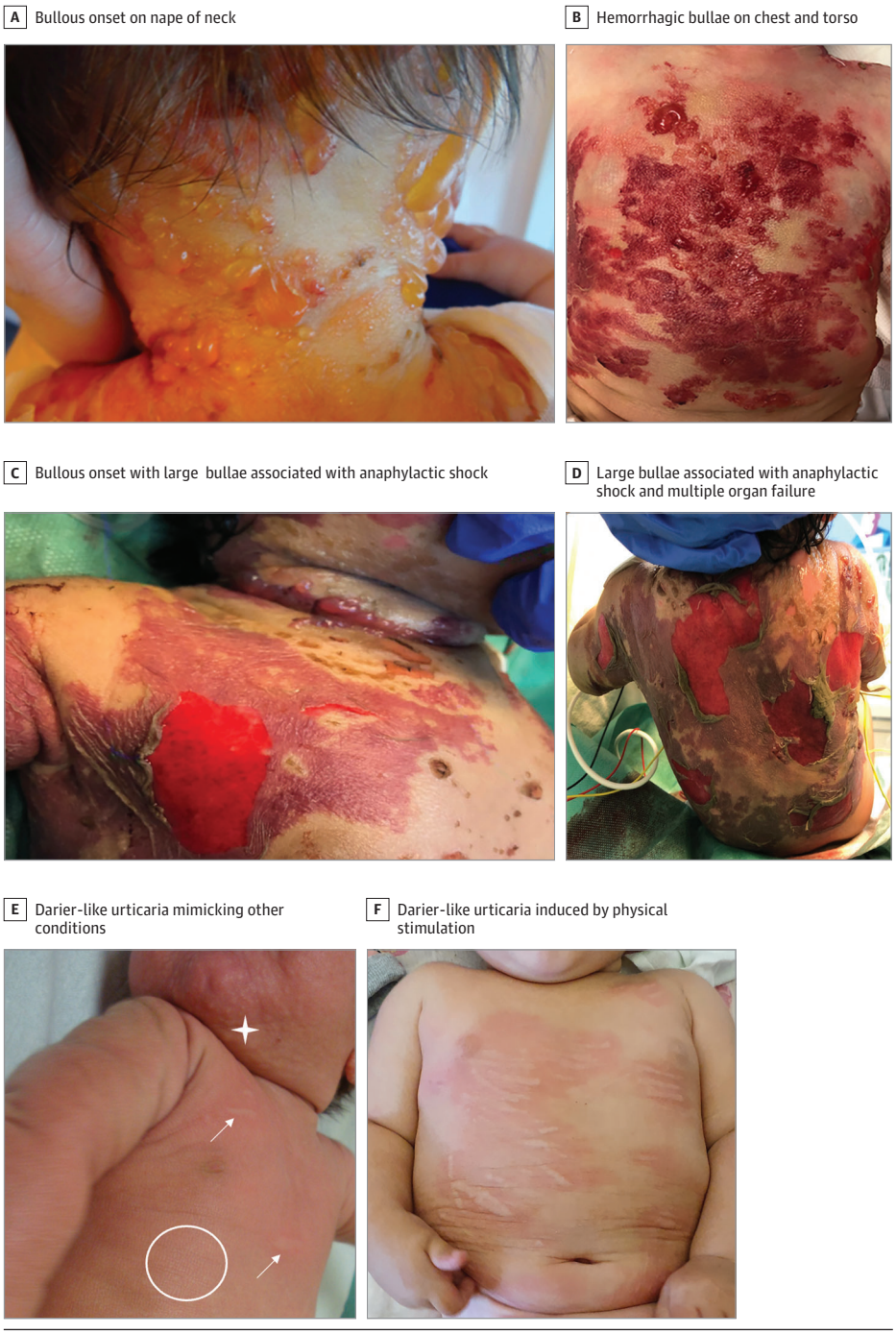
[b] Patients who presented with ASM had their diagnosis confirmed by bone marrow examination and the presence of C-finding criteria. Additionally, for 1 patient with CM, bone marrow exploration was not performed.

[c] Patient 3 began systemic treatment in adulthood after being lost to follow-up during childhood, with follow-up resuming after hepatic fibrosis and esophagitis developed.

[d] Patient 4 died from an incident unrelated to the treatment (accidental death/trauma).

[e] Patient 7 discontinued imatinib after 2 weeks because of a bullous eruption, which was considered unrelated to the treatment. After this flare-up, the treatment was not continued due to a notable improvement in MC activation symptoms.

Figure. Cutaneous Characteristics of Study Participants



A-B, Bullous onset with hemorrhagic bullae in 1 patient. C-D, Bullous onset with large bullae associated with anaphylactic shock and complicated by multiple organ failure in another patient (patient 5). E, Darier-like urticaria mimicking dermographism (arrows), *peau d'orange* (circle), and skin infiltration (star) in a patient with progressive-onset DCM. F, Darier-like urticaria induced by physical stimulation in a patient with progressive-onset DCM.

D816V status (eTable 3 in Supplement 1). Detection of the *KIT* D816V variant in blood using highly sensitive techniques may help identify patients at higher risk at diagnosis.

Most patients (78.8%) received nontargeted treatments such as H1 antihistamines (eg, desloratadine), with or without H2 antihistamines, montelukast, and/or sodium cromoglycate. Short courses of corticosteroids (1 month) were used during significant bullous flares. For skin care, we recommend topical steroids at flare onset, H1 and/or H2 antihistamines to relieve pruritus and prevent flares, and avoidance of triggers such as temperature fluctuations and friction. DCM tended to regress earlier than MPCM, and parents can be reassured about its favorable outcome in the absence of systemic involvement, as bullous episodes typically resolve by 34 months. For patients without *KIT* D816V-positive mastocytosis, imatinib was effective and well tolerated.[10-12] Although midostaurin was the standard TKI for adults with advanced SM until the approval of selective TKI, only 1 other report demonstrated its

effectiveness and safety in an infant with indolent SM.[13] We also reported sirolimus as effective and well tolerated in 2 children with *KIT* D816V-positive ASM, consistent with recent adult data.[14] It may represent an alternative to midostaurin, especially given its good pediatric tolerance.[15]

Limitations

This was a retrospective observational study with a small sample size. It had a single-center design with potential selection bias, including a higher proportion of patients with severe disease.

Conclusions

In this cohort study, DCM presentation differs significantly from MPCM. A clinical presentation of DCM may be associated with an increased risk of ASM and anaphylaxis, each occurring in 12.1% of patients in the present DCM cohort. Aggressive systemic forms were consistently associated with the *KIT* D816V variant. TKIs and sirolimus were generally effective and well tolerated in this pediatric population, with treatment selection dependent on the type of *KIT* variants.

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