Original Article

Clinicopathological Profile of Childhood Onset Cutaneous Mastocytosis from a Tertiary Care Center in South India

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Abstract

Background: Mastocytosis is characterized by clonal proliferation of mast cells in various organs and can have isolated cutaneous or systemic involvement. Childhood-onset mastocytosis (COM) is usually cutaneous and regresses spontaneously, while adult-onset mastocytosis (AOM) is often persistent with systemic involvement. There is limited data on COM from India. **Objective:** To elucidate the clinicopathological profile of COM. **Methods:** We conducted a retrospective chart review of all the patients with histologically proven COM (≤16 years), presenting over 11 years (January 2009 to December 2019) to the Dermatology Department. We compiled the demographic data, clinical characteristics (morphology, extent, distribution), laboratory investigations, histopathology findings, imaging (ultrasound abdomen), *c-KIT* mutation results, where available, and other associated abnormalities, and grouped them according to the WHO classification for mastocytosis. **Results:** Among the 66 patients with COM (M: F–1.6:1), 89.4% had onset before 2 years of age. The subtypes were: maculopapular cutaneous mastocytosis (MPCM: 44, 66.7%); mastocytoma of the skin (MOS: 19, 28.8%); diffuse cutaneous mastocytosis (DCM: 2, 3%) and indolent systemic mastocytosis (ISM: 1, 1.5%). Blistering was observed in 29 (43.9%) and Darier sign was elicited in 47 (71.2%) patients. Serum tryptase was elevated in 9/21 (42.9%) patients, but none had systemic mastocytosis. Three patients had *c-KIT* mutations (two in exon 8 and one in exon 17). Most patients were managed symptomatically and the patient with ISM improved with imatinib. **Conclusion:** MPCM is the most common variant of COM and most patients had a disease onset before 2 years. Overall, COM had a good prognosis with rare systemic involvement, mitigating the need for extensive evaluation routinely in children.

Keywords: *Childhood mastocytosis, c-KIT, cutaneous mastocytosis, mastocytoma, pediatric mastocytosis, tryptase, urticaria pigmentosa*

Introduction

Mastocytosis is characterized by clonal proliferation of mast cells (MC) in various organs. Childhood-onset mastocytosis (COM) presents before 2 years of age in 90% and in few at birth.[1] Adult-onset mastocytosis (AOM) develops between 20 and 35 years and is commonly associated with *c-KIT* mutations in exon 17.[2] Childhood mastocytosis can be associated with activating mutations in *c-KIT*, involving exons 8, 9 or 11 in addition to those affecting exon 17.[2,3] In 2–4% of the cases, mastocytosis can be familial with at least one first-degree relative being affected.[4]

In cutaneous mastocytosis (CM), only the skin is involved, whereas in systemic mastocytosis (SM), the extracutaneous organs are affected with/without cutaneous involvement. The updated WHO classification (2016)[5] is described in Table 1. Around two-thirds of the cases have childhood-onset disease,[1] which is generally confined to the skin, whereas systemic involvement is common in adults.[3] Of the three variants of CM, maculopapular CM (MPCM)/urticaria pigmentosa (UP) is the commonest (70–90%), followed by mastocytoma of the skin (MOS) (10–30%) occurring exclusively in children. Diffuse cutaneous mastocytosis (DCM) is extremely rare, manifesting at birth or early infancy (1–3%).[6] Though, the diagnosis is often clinical; histopathological, biochemical, and genetic tests can aid in the diagnosis and management. COM shows spontaneous, partial, or complete remission in 67% of

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Table 1: Updated WHO* 2016 mastocytosis classification[5]

*WHO classification	Variant	Our study (*n*=66) *n* (%)
Cutaneous mastocytosis (CM) (*n*=65)	Maculopapular CM (MPCM) = Urticaria pigmentosa (UP)	44 (66.7)
	Diffuse CM (DCM)	2 (3)
	Mastocytoma of skin (MOS)	19 (28.8)
Systemic mastocytosis (SM) (*n*=1)	Indolent systemic mastocytosis (ISM)	1 (1.5)#
	Smoldering systemic mastocytosis	0
	SM with associated hematologic neoplasm	0
	Aggressive SM	0
	Mast cell leukemia	0
Mast cell sarcoma (*n*=0)		0

*WHO, World Health Organization; #the patient with ISM had associated MPCM

the cases,[1] often by puberty, whereas AOM frequently persists.[3]

Despite available literature from various parts of the world, there is a paucity of data from India. We attempted to elucidate the clinicopathological profile of COM among Indians.

Methods

We conducted a retrospective chart review of all patients with histologically established childhood-onset (≤16 years) mastocytosis presenting between January 2009 and December 2019 (11 years) to the Dermatology Department, using the hospital database. Details on the demography, clinical profile, systemic involvement, histopathology, laboratory investigations, imaging, and treatment were abstracted. The study was approved by the Institutional Review Board (IRB No: 12329, dated 24th June 2020).

The patients were categorized based on the updated WHO classification[5] [Table 1]. MPCM presents with red-brown macules, papules, plaques, and telangiectasia. MOS is characterized by solitary brown to yellowish nodules or papules/plaques up to a maximum of 3 lesions, whereas ≥4 lesions are categorized as MPCM.[7] DCM is defined by generalized thickening of the skin without individual hyperpigmented cutaneous lesions. All the cases were confirmed histologically using toluidine blue stain and CD117 staining was done if the metachromatic stain was inconclusive, as it is more sensitive and helps to detect even minimal, loosely scattered, and atypical MC. MC degranulation can happen during skin biopsy and CD117 can highlight the hypogranulated MC which may not stain with metachromatic stains (Giemsa and toluidine blue).[8]

All the patients had full blood count and liver function tests. Abdominal ultrasound was performed to check if there was transaminitis or clinical suspicion of organomegaly. The facility for serum tryptase measurement was available since May 2015 and was done for consenting patients with extensive skin disease. Patients with severe disease, persistent systemic symptoms with high tryptase, or organomegaly underwent bone marrow examination. The DNA extracted from the skin tissue of seven patients with extensive disease (MPCM-6, DCM-1) and DNA from the peripheral blood of the patient with ISM were used to amplify c-KIT exon 8 and 17 by polymerase chain reaction (PCR) followed by Sanger sequencing using the previously reported protocols.[9]

Statistical analysis was done using SPSS, version 21. The baseline characteristics of the patients were analyzed by descriptive statistics. The categorical data were described using percentages and frequencies.

Results

During the study period, 110 patients were clinically suspected as COM, of whom 66 with histopathologically proven COM were recruited into the study [Figure. 1].

There were 41 males, 25 females (M:F - 1.6:1) with COM and the mean and median age at presentation was 3.9 years (SD = 5.3) and 2 years, respectively (range 1 month to 29 years). The disease onset ranged from birth to 12 years, with a mean and median of 14 months (SD, 32.9 months) and 3 months, respectively. In 59 (89.4%) patients, the disease presented before 2 years of age and 17 (25.8%) had lesions at birth.

The frequencies of the mastocytosis subtypes and the clinical profile of CM are shown in Tables 1 and 2, respectively. MPCM [Figure. 2 a–e] was the most common subtype, followed by MOS [Figure. 2 f], and DCM [Figure 2 g, h]. MPCM commonly presented as erythematous or hyperpigmented macules or maculopapules (81.8%). The plaque type MPCM was reported in 15.9%, of whom 3/44 (6.8%) had yellowish plaques (xanthelasmoid mastocytosis). Telangiectasia macularis eruptive perstans (TMEP), a variant of MPCM, was seen in only 1 out of 44 (2.3%) patients with MPCM; and this patient had telangiectatic macules involving the face and trunk.

The various signs and symptoms of CM at presentation are tabulated in Table 3. Systemic symptoms were reported by 12 (18.2%) patients, including the patient with ISM. The

Table 2: Clinical profile of the patients with childhood-onset cutaneous mastocytosis

Clinical presentation	Total (*n*=66) *n* (%)	MPCM (*n*=44) *n* (%)	DCM (*n*=2) *n* (%)	MOS (*n*=19) *n* (%)	SM (*n*=1) *n* (%)
Male: Female	1.6:1	1.5:1	2F	2.8:1	1F
Age at onset of disease					
Disease onset at birth	17 (25.8)	6 (13.6)	1 (50)	10 (52.6)	0
Disease onset before 2 years	59 (89.4)	38 (86.3)	2 (100)	18 (94.7)	1 (100)
Cutaneous presentation					
Macular or maculopapular	37 (56.0)	36 (81.8)	0	0	1 (100)
Plaque	18 (27.3)	7 (15.9)	0	11 (57.9)	0
Papule	4 (6.1)	0	0	4 (21.1)	0
Nodule	4 (6.1)	0	0	4 (21.1)	0
Extensive skin infiltration	2 (3.0)	0	2 (100)	0	0
Telangiectasia	1 (1.5)	1 (2.3)	0	0	0
Site of involvement					
Face	3 (4.5)	0	0	3 (15.8)	0
Trunk	14 (21.2)	4 (9.1)	0	10 (52.6)	0
Face and Trunk	3 (4.5)	2 (4.5)	0	1 (5.3)	0
Buttock and extremities	6 (9.1)	1 (2.3)	0	5 (26.3)	0
Generalized involvement	40 (60.6)	37 (84.1)	2 (100)	0	1 (100)

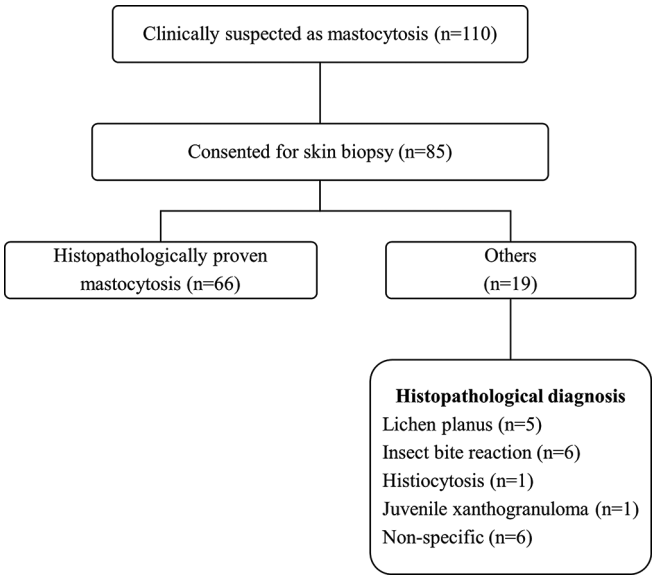

Figure 1: Patient flow chart.

most common cutaneous symptom was itching (74.2%), and the systemic symptom was gastrointestinal in 12.1% (abdominal pain and diarrhea) followed by respiratory symptoms in 6.1%.

Among the 66 patients with COM, one progressed to ISM with bone marrow involvement. She had cutaneous manifestations (itching, wheals, blistering) from 6 months of age followed by progressive, persistent systemic symptoms (wheezing, giddiness, and angioedema) and was diagnosed as ISM at 19 years of age (published previously).[10]

Investigations

The various investigations are tabulated in Table 4.

Laboratory investigations

Anemia (Hb <10 gm/dL) was seen in 23.1% of the patients. Mild eosinophilia (0.5–1.5 × 10^9/L) was present in 32.7% of the patients and 1.7% had severe eosinophilia (>1.5 × 10^9/L). Among the 12 patients who had systemic symptoms, only 4 (33.3%) had eosinophilia and none with eosinophilia had organomegaly.

High-serum tryptase level (>24 ng/mL) was seen in 9/21 (42.9%) patients (MPCM: 4, MOS: 5), of whom four had extensive involvement and one had diarrhea. Among the 12 patients with normal tryptase levels, 1 had systemic symptoms (recurrent abdominal pain). Serum tryptase assessment was not done in the patient with ISM as this facility was unavailable then.

Ultrasound abdomen

Among patients with MPCM (*n* = 44), one had hepatomegaly.

Histopathology

Skin: The various histopathological patterns [Figure. 3 a–d] seen in CM are shown in Table 4. In our cohort, diffuse mast cell infiltrates in the papillary and upper reticular dermis were seen in 36.3%. Toluidine blue was positive [Figure. 3 e] in all the patients (strongly positive: 48/66, weakly positive: 18/66). Those with weak toluidine blue staining (18/66), highlighted MC well on CD117 staining [Figure. 3 f].

Bone marrow examination: This was performed in three patients of whom only one had multifocal dense infiltrates of MC (≥15 MCs in aggregates) positive for CD25 suggestive of ISM, whereas the other two were normal.

Table 3: Mast-cell-mediated symptoms and signs

Symptoms and signs	Total (*n*=66) *n* (%)	MPCM (*n*=44) *n* (%)	DCM (*n*=2) *n* (%)	MOS (*n*=19) *n* (%)	SM (*n*=1) *n* (%)
Itching	49 (74.2)	32 (48.4)	2 (100)	14 (73.6)	1 (100)
Recurrent abdominal pain	6 (9.1)	5 (11.3)	0	1 (5.2)	0
Diarrhea	2 (3.0)	1 (2.2)	0	1 (5.2)	0
Headache, dizziness	1 (1.5)	0	0	0	1 (100)
Dyspnea	3 (4.5)	3 (6.8)	0	0	0
Cough, recurrent sinopulmonary infections	1 (1.5)	1 (2.2)	0	0	0
Angioedema	1 (1.5)	0	0	0	1 (100)
Blistering of skin	29 (43.9)	14 (31.8)	2 (100)	12 (63.1)	1 (100)
Darier sign	47 (71.2)	28 (63.6)	2 (100)	16 (84.2)	1 (100)

*Systemic symptoms were reported in 12 patients of whom two had more than one systemic symptom.

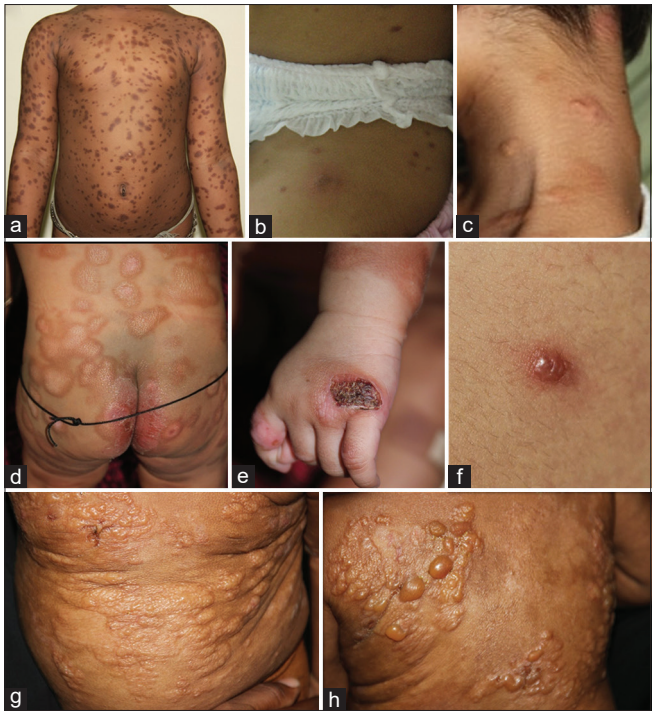

Figure 2: (a) Multiple light brown to hyperpigmented macules in a patient with MPCM, (b) positive Darier sign in MPCM, (c) yellowish pseudoxanthomatous plaques on the neck of a patient with MPCM, (d) diffuse MPCM with multiple plaques, (e) MPCM with plaques showing blistering and ulceration, (f) solitary mastocytoma of the skin with positive Darier sign, (g) diffuse infiltration of the skin (h) with blistering in diffuse cutaneous mastocytosis.

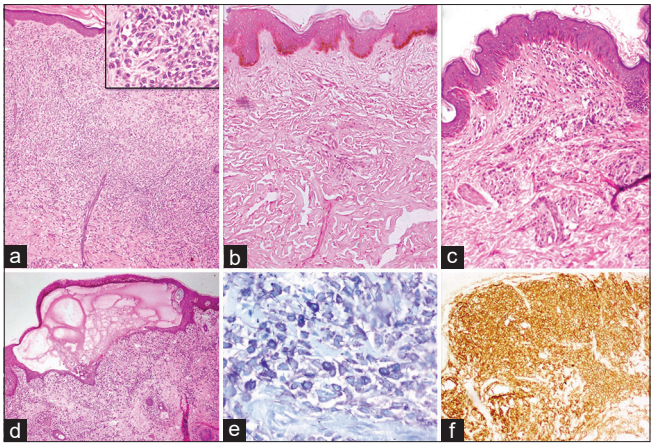

Figure 3: Histopathology showing (a) dense diffuse infiltrates of mast cells in the upper third of the dermis (H and E, 50X), insert (H and E, 100X); (b) telangiectasia with mild perivascular infiltrates of lymphocytes and scattered mast cells in the superficial dermis, basal layer hyperpigmentation (H and E, 100X); (c) proliferated blood vessels with moderate aggregates of mast cells admixed with occasional lymphocytes and histiocytes (H and E, 100X); (d) intraepidermal bulla with diffuse and perivascular aggregates of mast cells in the dermis (H and E, 50X) (e) Mast cells highlighted using toluidine blue stain (200X); (f) CD117 positive mast cells (immunoperoxidase stain, 100X)

c-KIT mutation analysis

c-KIT variants in exons 8 or 17 were found in three patients [Table 5] but negative in the patient with ISM. The Sanger sequencing electropherogram of the *c-KIT* mutations identified in this study is depicted in Figure 4.

Treatment and follow-up

All patients were educated and were given a list of triggers to avoid. Four patients did not require treatment as the disease was quiescent at presentation, whereas the others received antihistamines. Thirty-eight patients required moderately potent topical steroids at the first visit. The clinical response was assessed during the subsequent visit. The mean duration of follow-up in our study was 9 ± 23 months; median: 3 weeks (range: 0–12 years). Twelve patients were lost to follow-up after the first visit, 26 (39.4%) improved with antihistamines and topical steroids, whereas 27 (40.9%) improved on further optimization of the antihistamines or addition of other treatment. Three with severe MPCM also received phototherapy. One of the children with DCM was treated with systemic steroids during an acute exacerbation. Two patients with DCM and one with ISM required hospitalization. One child with DCM, admitted with sepsis, was inadvertently administered vancomycin, which led to increased blistering and improved drastically on drug withdrawal. Since most of our patients were from distant places, we had inadequate data on the regression or resolution rates. The last follow-up of the children with DCM was at 4.5 and 8.5 years of age and the skin infiltration had decreased. The patient with ISM and

Table 4: Investigations

Investigation (*n*=number of patients for whom results were available)	Total *n* (%)	MPCM *n* (%)	DCM *n* (%)	MOS *n* (%)	SM *n* (%)
Hemoglobin (*n*=61)	*n*=61	*n*=42	*n*=2	*n*=16	*n*=1
<10 gm/dL	16 (23.1)	10 (23.8)	0	6 (37.5)	0
10-12 gm/dL	24 (39.3)	15 (35.7)	0	8 (50)	1 (100)
>12 gm/dL	21 (34.4)	17 (40.4)	2 (100)	2 (12.5)	0
Eosinophil count (*n*=58)	*n*=58	*n*=42	*n*=2	*n*=13	*n*=1
< 0.5×10^9/L	38 (65.5)	26 (61.9)	2 (100)	9 (69.2)	1 (100)
0.5-1.5×10^9/L	19 (32.7)	15 (35.7)	0	4 (30.8)	0
>1.5×10^9/L	1 (1.7)	1 (2.4)	0	0	0
Liver enzymes-AST/ALT (*n*=58)	*n*=58	*n*=39	*n*=2	*n*=16	*n*=1
Normal (<40 U/L)	47 (81)	34 (87.1)	2 (100)	10 (62.5)	1 (100)
<3 times above normal value	10 (17.2)	5 (12.8)	0	5 (31.2)	0
>3 times above normal value	1 (1.7)	1 (2.5)	0	0	0
Serum tryptase (*n*=21)	*n*=21	*n*=13	*n*=0	*n*=8	*n*=0
Normal (<24 ng/ml)	12 (57.1)	9 (69.2)	0	3 (37.5)	0
High (>24 ng/ml)	9 (42.9)	4 (30.8)	0	5 (62.5)	0
Ultrasound abdomen (*n*=31)	*n*=31	*n*=20	*n*=1	*n*=9	*n*=1
Normal	30 (96.7)	20 (100)	1 (100)	8 (88.8)	1 (100)
Hepatomegaly	1 (3.2)	0	0	1 (11.1)	0
Histopathological pattern (*n*=66)	*n*=66	*n*=44	*n*=2	*n*=19	*n*=1
Diffuse mast cell infiltrates in the dermis	24 (36.3)	16 (36.3)	1 (50)	7 (36.8)	0
Perivascular mast cell infiltrates in the dermis	19 (28.7)	13 (29.5)	0	6 (31.5)	0
Interstitial and perivascular mast cell infiltrates in the dermis	16 (24.2)	9 (20.4)	1 (50)	5 (26.3)	1 (100)
Nodular mast cell infiltrates in the dermis	7 (10.6)	6 (13.6)	0	1 (5.2)	0

AST - Aspartate transaminase, ALT - Alanine transaminase

Table 5: c-KIT mutation among patients with childhood-onset cutaneous mastocytosis

c- KIT (Transcript/Exon)	cDNA	Amino Acid	Type of CM	Age at onset	Systemic symptoms	Organomegaly	Mast cell tryptase level ng/ml	Bone marrow biopsy
NM_000222.3 (KIT_v001)/Exon 8	c. 1250_1256delCTTACGAinsT (deletion-insertion resulting in an in-frame mutation)/Novel	p.(Thr417_ Asp419delinsIle)	MPCM	2 days of birth	Nil	Absent	10.9	Not done
NM_000222.3 (KIT_v001)/Exon 8	c. 1255_1257delGAC (in-frame deletion)	p.(Asp419del)	DCM	3 months	Nil	Absent	Not done	Not done
NM_000222.3 (KIT_v001)/Exon 17	c. 2447A>T (missense mutation)	p.(Asp816Val)	MPCM	3 months	Nil	Absent	24	Not done

negative *c-KIT* mutation was treated with imatinib. Her skin lesions regressed in 4 months and a repeat bone marrow examination at 20 weeks ruled out residual disease.[10]

Discussion

The incidence of mastocytosis varies from 1:1000 to 1:8000,[6] however, the exact incidence among Indians is unknown. Approximately 1,324 new cases are seen in our Pediatric Dermatology Clinic per year. As per our data, there are six cases of COM per year, which contribute to 0.45% of our new patients. The proportion of the subtypes is also subject to ascertainment bias as a mild disease may not present to us and SM would be managed by haemato-oncologists.

We have compared our results with the literature[1,11-16] [Table 6]. In our series, congenital onset of CM was seen in 25.8% and 89.4% had disease onset before 2 years of age with slight male preponderance (1.6:1) as reported previously.[1,12-14]

MPCM represents approximately 70–90% of all pediatric cases in various studies[1,11,13,16] and 80–90% manifest by 1 year of age.[11,13-15] Similarly, MPCM was the commonest subtype (66.7%) in our study and 89.4% of them had disease onset before 2 years of age. It has been postulated that neither type nor the extent of the disease is predictive of systemic involvement,[17] as evident in our study. As reported by Meni *et al*.,[1] most patients presented as maculopapular

Table 6: Comparison between the present study and previous studies on cutaneous mastocytosis

Criteria	India Present study	Systematic Review Meni *et al*.[1]	Poland Lange *et al*.[11]	Israel Ben Amitai *et al*.[12]	Mexico Kiszewski *et al*.[13]	Australia Hannaford and Rogers[14]	Spain Azana *et al*.[15]	India Kanwar AJ, Sandhu K[16]
Number of cases	66	1747	101	180	71	173	67	17#
Duration of study (years)	11	NA	7	20	28	-	-	14
Type of study	R	R	P	R	R	R	P	R
Male: female ratio	1.6:1	1.4:1	1.2:1	1.5:1	1.8:1	1.3:1	1:1.03	1:1.1
Age of onset (%)								
Congenital	25.8	23	31	-	-	24	25.4	0
<1 year	83.3	-	94	-	92	92	83.6	NA
<2 years	89.4	90	97	92.7	-	-	92.5	58.8
Variants (%)								
MPCM/UP	66.7	74.8	84	65	75	47	All cases	64.7
MOS	28.8	19.5	10	34.4	17	51	NA	17.6
DCM	3	5.2	6	0.6	8	2	NA	5.9
Itching (%)	74.2	48	68	-	61	-	62.7	100
Darier sign	71.2	91	100	-	94	-	92.5	-
Blistering (%)								
Overall	43.9	34.5	25	-	22.5	28.3	NA	17.6
MPCM/UP	31.8	-	21.4	24	27.8	23	25.4	18.2
MOS	63.1	-	100	33	40	31	NA	33.3
DCM	100	-	10	-	80	66	NA	0

P, prospective; R, retrospective; NA, not applicable. #Includes two patients classified as bullous mastocytosis as a clinical variant

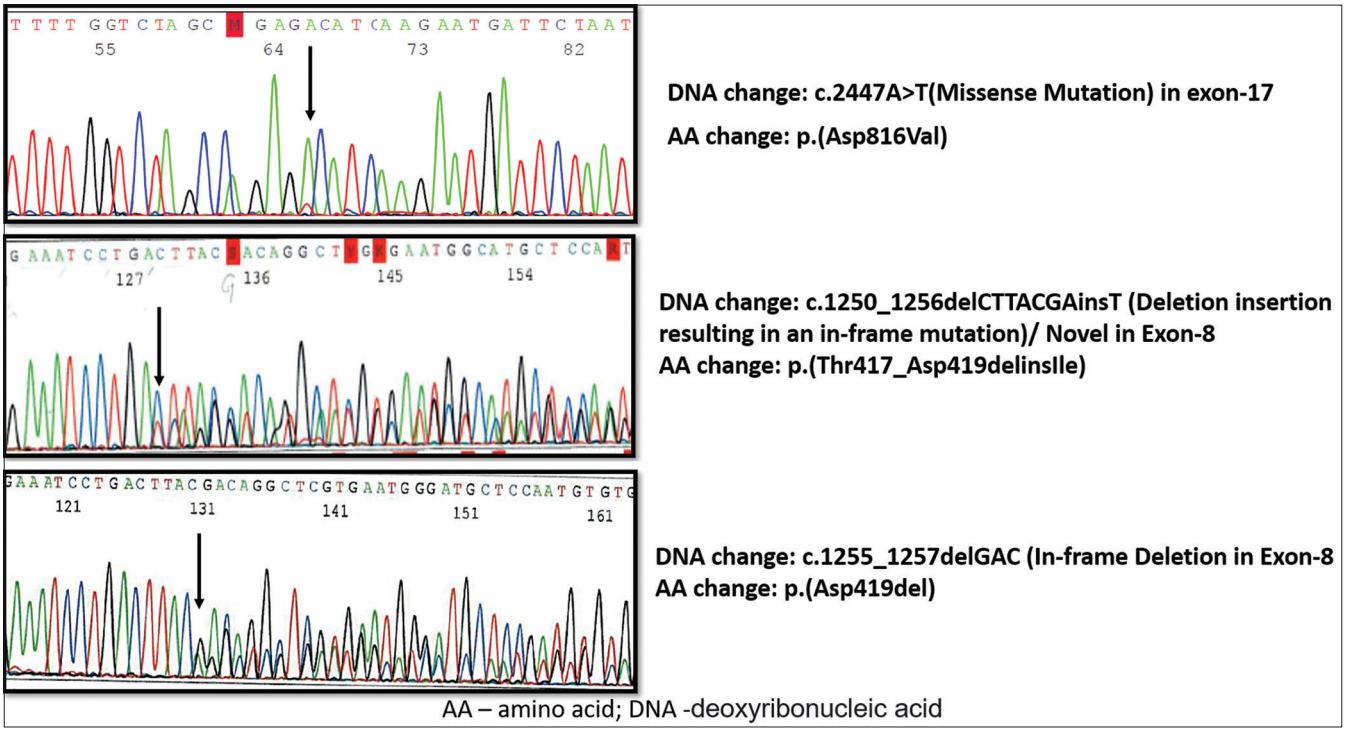

Figure 4: Sanger sequencing electropherogram of the *c-KIT* mutations identified in exon 17 and 8 in this study.

lesions in our study. Although TMEP is not recognized in the WHO classification, some consider it under MPCM.[18] It is common in adults and seen in only 0.3% of children[1] and there was only one pediatric-onset TMEP in our study. MOS commonly involved the upper trunk (52.6%), similar to the Australian study (54%).[14] The prevalence of MOS could be less, as many do not report to hospital and some may regress spontaneously. In our series, only one patient had ISM which is similar to that reported by Lange *et al*.[11]

Darier sign, a sensitive but not specific marker for mastocytosis, was elicited in 71.2% of our patients, similar

to 91% reported by Meni *et al*.[1] In our study, blistering was the cutaneous complication most commonly recorded. Studies have reported blistering as high as 66–100% in DCM[13,14,19] and 100% in MOS.[11] We noted blistering in all DCM patients (100%) and 63.1% MOS.

CM can present with heterogeneous systemic symptoms due to the release of chemicals such as histamine, tryptase, prostaglandins, and leukotrienes following mast cell degranulation.[4] DCM cases are at a high risk of serious consequences like anaphylaxis, hemorrhage, and cardiovascular collapse.[19] While only 12.1% of our cohort had gastrointestinal symptoms, Meni *et al*.[1] reported this in 19.5% of the children with mastocytosis. Respiratory symptoms were reported in 6.1%, closer to that reported by Ben Amitai *et al*. (10.3%).[12] Hematological abnormalities are commonly reported with SM and are an indicator of bone marrow involvement. Though anemia was seen in 23.1% of our patients, they did not have features suggestive of SM. Anemia could be attributable to other causes such as nutritional deficiency which is common in developing countries. Kiszewski *et al*.[13] reported anemia in 21.4% with COM. In a study done by Kluin-Nelemans *et al*.,[20] eosinophilia was frequently observed in advanced SM when compared to ISM and CM. Sex (women more than men), age, the WHO classification, dysmyelopoiesis, *KIT* mutation positivity, lymphadenopathy, and organomegaly had a significant positive correlation with eosinophilia, but there was no correlation with mediator-related symptoms or allergies.[20] In our study, 33.3% with systemic symptoms had eosinophilia. None of our patients with eosinophilia had organomegaly and the patient with ISM did not have eosinophilia at presentation.

It has been proposed that the extent of skin involvement is not directly associated with local or systemic symptoms.[17] In our study, 20% of the patients with extensive disease had systemic symptoms including the patient with ISM. Organomegaly was seen only in 3.2% of our patients which is fewer than that reported by Lange *et al*.[11] (10% with hepatomegaly) and Kiszewski *et al*.[13] (17.3% with hepatomegaly and 6.5% with splenomegaly).

The various histopathological patterns of mastocytosis described include perivascular MC infiltration in papillary, upper reticular dermis; sheet-like MC infiltrate in the upper dermis; interstitial, and nodular pattern.[21] Diffuse mast cell infiltrate in the papillary, upper reticular dermis was the commonest pattern (36.4%) in our study. Despite the various clinical presentations, the histological hallmark is the same for all types of CM and skin biopsy does not identify the clinical pattern, which was evident in our study.[21]

Mast cell tryptase level >20 ng/mL is one of the minor criteria[5] to diagnose SM. Sperr *et al*.[22] reported high tryptase levels in 13% of the CM as opposed to 42.9% in ours. Lange *et al*.[11] found a positive correlation between serum tryptase level and symptoms such as extensive blistering, flushing, hypotension, diarrhea, and osteoporosis/osteopenia. High serum tryptase levels correlate with extensive skin involvement,[23] but do not have a significant prognostic value in childhood mastocytosis.[1] There was no correlation between the extent of involvement and serum tryptase in our study (P = 0.2) and we were unable to correlate between the morphological type and serum tryptase levels as the level was not estimated in all our patients due to various factors (unavailability of the test in the beginning and financial constraints). Further prospective studies of a larger series of patients might help to determine this correlation.

Most *c-KIT* mutations in mastocytosis are located in exon 17 and are mostly missense point mutations, the commonest being D816V.[3] The *KIT* D816V point mutation is present in approximately 80% of the adults with mastocytosis.[2] Bodemer *et al*.[3] found *c-KIT* activating mutations from skin biopsies in 86% of the children with mastocytosis; at codon 816 in 42% (of which 36% were D816V) and outside exon 17 (exon 8, 9, 11) in 44%, but there was no phenotype-genotype correlation. In the systematic analysis by Meni *et al*.,[1] 34% had mutations in exon 17 including D816V and 18% had mutations outside exon 17 and there was no correlation between the *KIT* mutation and disease outcome. Lanternier *et al*.[24] reported three SM patients with Del419D in exon 8 of whom two patients had COM and one had the adult-onset disease. This mutation was seen in one of our patients with DCM. Of the two exon 8 mutations identified, a complex indel (deletion-insertion) (c. 1250_1256delCTTACGAinsT) resulting in an in-frame deletion was identified in a patient with MPCM. This mutation has been reported in a case of adult AML with t (8;21).[25] However, to the best of our knowledge, this mutation has not been reported in CM so far. Though *KIT* D816V point mutation is commonly seen in SM, this was not seen in our patient with ISM, rather it was seen in MPCM.

Due to the usual benign and self-limiting nature of CM, aggressive therapies are avoided.[1] Almost all patients (82.2%, 57/62) in our study received conservative management and the patient with ISM with negative *c-KIT* mutation responded to imatinib. The identification of the mutation can help in management, as D816V *KIT* mutation renders neoplastic MC resistant to imatinib and is useful in patients with advanced SM with negative *c-KIT* mutations or mutations outside of exon 17.[10]

Limitation

Since our study was retrospective, data were not uniform. Some investigations including serum tryptase, c-*KIT* mutation analysis were not done for all the patients due to financial constraints and long-term follow-up was not available for many patients.

Conclusion

The most common variant of CM was MPCM and most patients had disease onset before 2 years. Overall, COM had a good prognosis with rare systemic involvement, mitigating the need for extensive evaluation routinely. However, long-term follow-up studies are essential to really understand the evolution of COM. Determining the location of *c-KIT* mutation helps to determine if drugs like imatinib would be useful in the management of severe disease. Also, exploring the *KIT* mutations associated with COM might help in a better understanding of the pathophysiology of the disease, prognosis, and management.

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Conflicts of interest

There are no conflicts of interest.

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