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Mastocytosis: A case series of 107 consecutive patients

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Mastocytosis is classified by the World-Health-Organisation (WHO)[1] as cutaneous-mastocytosis (CM) and systemic-mastocytosis (SM). CM is subdivided into maculopapular (MPCM), diffuse-CM and mastocytomas. SM is subdivided into indolent (ISM), with-an-associated-haematologic-neoplasm (SM-AHN)[2], aggressive (ASM) and mast-cell-leukemia (MCL).

Mastocytosis is rare, with poorly established epidemiology. Specific indicators of disease progression would be useful in SM, especially in atypical cases. The management of mastocytosis is largely symptomatic and based on extrapolation from small series and expert opinion in allergic disease.

This retrospective review describes 107 adults with mastocytosis seen at our large tertiary centre in Australia between January 1995 to March 2015. We aimed to; establish the epidemiology, clinical, laboratory and management features of mastocytosis at our Australian centre; describe and compare MPCM and ISM; describe key therapeutic outcomes. Patients with mastocytosis were identified using a pre-established prospective database of patients categorised utilising WHO-classification[1]. Treatment responses were scaled as no-response (NR), partial-response (PR; some improvement) and

complete-response (CR; no symptoms while on treatment). The study was approved by the Melbourne-Health-Human-Research-Ethics-Committee.

A total of 132 patients with mastocytosis were identified; medical records were only available for 109. Two of the 109 patients maintained their diagnosis of Telangiectasia-Macularis-Eruptiva-Perstans (TMEP) (removed from the 2008 WHO Diagnostic-Criteria)[1] during the study, hence were excluded. Table 1 summarises the main clinical, laboratory and management results.

A total of 95 (88.8%) patients were diagnosed with MPCM, 8 (7.5%) with ISM and 4 (3.7%) TMEP. During the study period this was revised to 54 (5.5%) MPCM, 50 (46.7%) ISM, 2 (1.9%) ASM and 1 (0.9%) SM-AHN due to bone marrow aspirate and trephine (BMAT) results. Of the 95 MPCM patients at presentation; 44 (46.3%) had ISM, 1 had ASM and the rest (50, 52.6%) maintained their diagnosis of MPCM. Of the 4 TMEP patients at presentation, 3 (75.0%) had ISM and 1 (25.0%) had MPCM. Of the 8 ISM patients at presentation, 1 (12.5%) had ASM, 1 (12.5%) SM-AHN and the rest (6, 75.0%) maintained their diagnosis of ISM.

BMAT was performed in 92 (86.0%) patients; 39 (27.2%) MPCM, 50 (100.0%) ISM, 2 (100.0%) ASM and 1 (100.0%) SM-AHN. The major diagnostic-criteria for SM was present in 44 (41.1%) patients; 43 (86.0%) ISM and 1 (50.0%) ASM. The remaining 7 ISM patients, 1 ASM and 1 SM-AHN patient met WHO diagnostic-criteria by fulfilling 3 minor criteria.

Diarrhoea was prevalent in 34 (68.0%) ISM but only 24 (44.4%) MPCM patients (p=0.02). Dyspepsia/nausea was prevalent in 37 (74.0%) ISM and 32 (59.3%) MPCM patients (p=0.1). Typical CM-skin lesions were clinically present in 52 (96.3%) MPCM and 40 (80.0%) ISM patients (p=0.09). The 2 MPCM patients without typical CM-skin lesions fulfilled 2 minor diagnostic-criteria.

Patients with ISM were significantly more likely to have osteopenia (n=29, 54.0%) or osteoporosis (n=10, 20.0%) compared to MPCM patients (n=15, 27.8%, p=0.006) and (n=2, 3.7%, p=0.01) respectively.

Regarding treatment, 3-times-weekly phototherapy was utilised in 31 (29.0%) patients and provided PR (n=9/19, 47.4%), NR (n=7/19, 36.8%) and CR (n=3/19, 15.5%) for pruritus and cosmesis.

Overall responses to cetirizine, fexofenadine, PPIs, ranitidine and sodium-chromoglycate are summarised in Figure 1. Cetirizine provided CR or PR for cutaneous (pruritus, flushing, cosmesis) (n=14/46, 30.4% or n=23/46, 50.0%), mediator-related (palpitations, dizziness, wheeze/dyspnoea, rhinorrhoea, headache and anaphylaxis) (n=4/13, 33.3% or n=0/13, 0.0%) and gastrointestinal (diarrhoea, dyspepsia, nausea/vomiting, abdominal-cramps) (n=3/20, 15.0% or n=8/20, 40.0%) symptoms. PPIs, ranitidine and sodium-chromoglycate were used for gastrointestinal symptoms. Ranitidine provided CR or PR in 92.1% (n=35/38 or n=15/38). PPIs provided CR 60.8% (n=31/51) and PR in 31.4% (n=16/51). All but one patient responded to sodium-cromoglycate (n=6 (85.7%)).

Montelukast was prescribed to 40-patients for neuropsychiatric-symptoms (mental-clouding and anxiety); providing CR (n=1/18, 5.6%), PR (n=3/18, 16.7%) and NR (n=14/18, 87.5%).

To our knowledge, this represents the largest study of adult patients with CM and SM within the Southern-Hemisphere. MPCM was the most prevalent subtype, followed by ISM, ASM and SM-AHNMD. Our study confirms that once investigated with BMAT, most patients with MPCM have ISM[3]. The current study found the prevalence of ISM in mastocytosis overall at 46.7%, consistent with 46.5%[4] and 32.0%[5] in other cohorts.

The most prevalent symptoms were cutaneous and gastrointestinal. Therefore, targeted management for these symptoms may improve quality-of-life in mastocytosis. The current study demonstrates that diarrhoea,

osteopenia and osteoporosis are significantly more prevalent in ISM compared to MPCM. Therefore a diagnosis of ISM should be particularly considered patients with MPCM suffering from diarrhoea, osteopenia or osteoporosis.

Cutaneous symptoms of mastocytosis responded well to antihistamines and phototherapy. Gastrointestinal symptoms responded to PPIs, ranitidine and sodium-chromoglycate. To our knowledge the efficacy of ranitidine and PPIs in the management of gastrointestinal symptoms in mastocytosis have not been previously documented.

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Table 1. Demographic, clinical, laboratory and management features of 107 patients with mastocytosis

Characteristics	No. of patients (%)	MPCM	ISM
Total no. of mastocytosis patients	107	54	50
Gender			
- Male	40 (37.4%)	19 (35.2%)	19 (38.0%)
- Female	67 (62.6%)	35 (64.8%)	31 (62.0%)
Clinical findings			
Symptoms (most prevalent to least)			
- Pruritus	85 (79.4%)	45 (83.3%)	37 (74.0%)
- Dyspepsia/ nausea	72 (67.3%)	32 (59.3%)	37 (74.0%)
- Diarrhoea	61 (57.0%)	24 (44.4%)	34 (68.0%)
- Flushing	54 (50.5%)	25 (46.3%)	27 (54.0%)
- Dizziness/ syncope	41 (38.3%)	16 (29.6%)	22 (44.0%)
- Bone pain	31 (29.0%)	13 (24.1%)	17 (34.0%)
- Wheeze/ SOB	29 (27.1%)	13 (24.1%)	15 (30.0)
- Headache	29 (27.1%)	14 (25.9%)	14 (28.0%)
- Rhinorrhoea	22 (20.6%)	13 (24.1%)	8 (16.0%)
- Mental clouding	19 (17.8%)	9 (16.7%)	9 (18.0%)
- Palpitations	18 (16.8%)	5 (9.3%)	12 (24.0%)
- Lethargy	16 (15.0%)	7 (13.0%)	9 (18.0%)
- Anxiety	15 (14.0%)	5 (9.3%)	9 (18.0%)

- Night sweats	10 (9.3%)	4 (7.4%)	5 (10.0%)
Signs			
- Classic CM skin lesion	94 (87.9%)	52 (96.3%)	40 (80.0%)
- Darrier's sign at presentation	47 (43.9%)	31 (57.4%)	14 (28.0%)
- Anaphylaxis	18 (16.8%)	8 (14.8%)	8 (16.0%)
Laboratory findings			
Tryptase at presentation > 20 ng/mL	57 (53.3%)	13 (24.1%)	41 (82.0%)
Max tryptase recorded >20ng/mL over the 20 year period	65 (60.7%)	15 (27.8%)	47 (94.0%)
Skin biopsy >20mc/ hpf	59 (55.1%)	54 (100.0%)	5 (10.0%)
Bone marrow aspirate	92 (86.0%)	39 (72.2%)	50 (100.0%)
- Dense multifocal aggregates (>15 mc/ aggregate)	44 (41.1%)	0 (0.0%)	43 (86.0%)
- >25% spindle shape mc	3 (2.8%)	2 (4.1%)	1 (1.8%)
c-KIT mutation	43 (40.2%)	7 (13.0%)	34 (68.0%)
CD2	30 (28.0%)	6 (11.1%)	22 (44.0%)
CD25	57 (53.3%)	11 (20.4%)	43 (86.0%)
Management			
Phototherapy	31 (29.0%)	18 (33.3%)	13 (26.0%)
Antihistamines			
- Cetirizine	88 (82.2%)	39 (72.2%)	46 (92.0%)
- Fexofenadine	40 (37.4%)	20 (37.0%)	20 (40.0%)
Monteleukast	40 (36.7%)	16 (29.6%)	22 (44.0%)
Sodium Chromogylcate	8 (7.3%)	3 (5.6%)	3 (6.0%)
Proton-pump inhibitor	67 (62.6%)	28 (51.9%)	36 (72.0%)
Ranitidine	62 (57.9%)	23 (42.6%)	37 (74.0%)

MPCM indicates maculopapular cutaneous mastocytosis; ISM, indolent systemic mastocytosis; ng, nanograms; mL, millilitre, mc, mast cells, hpf, high power field, %, percentage, max, maximum, DEXA, dual-energy x-ray absorptiometry

Figure legend

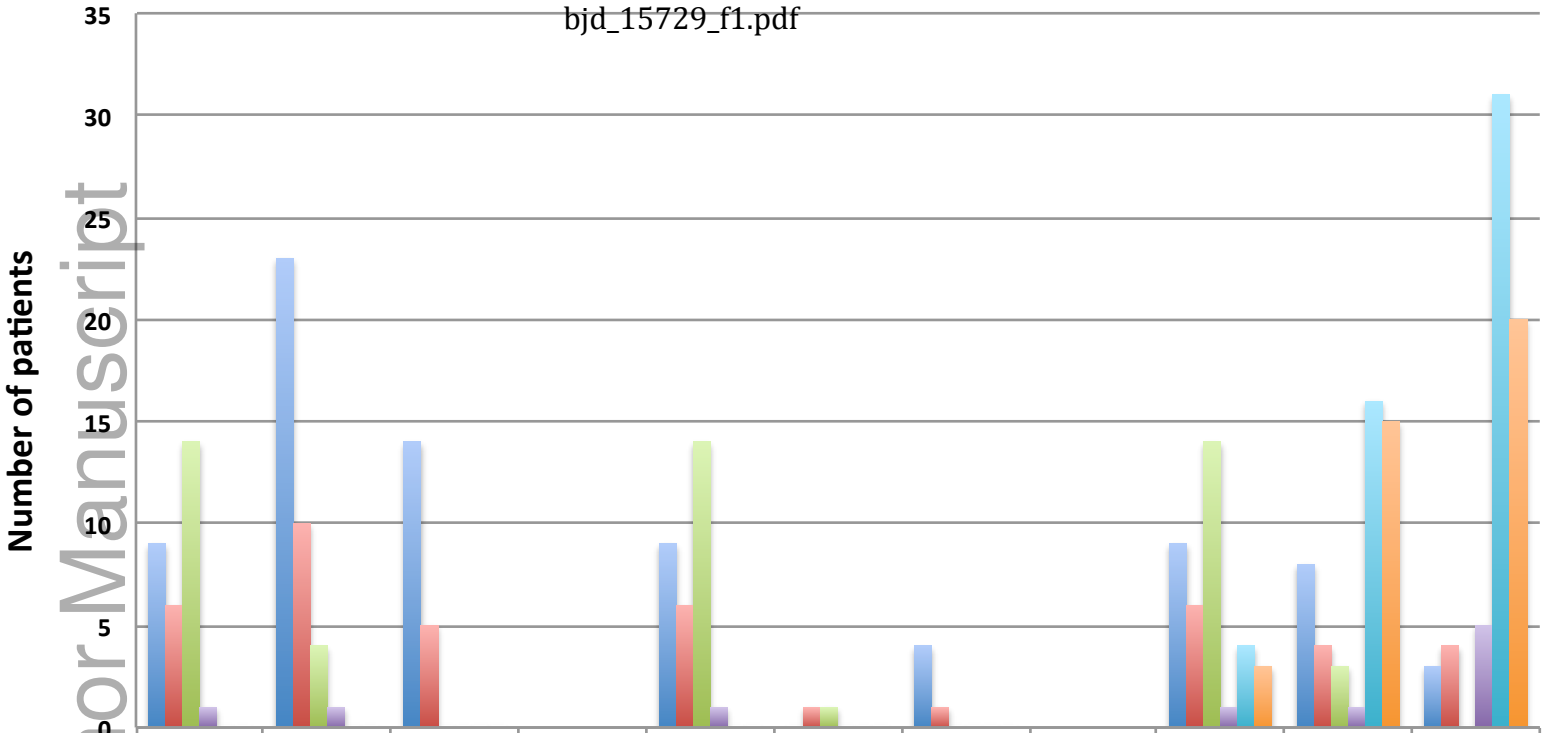
Figure 1 Response rates of cetirizine, fexofenadine, monteleukast, sodium chromoglycate, proton-pump inhibitors (PPIs) and ranitidine in the management of cutaneous*, mediator-related# and gastrointestinal^ (GIT) symptoms of mastocytosis

*= Classic cutaneous mastocytosis skin lesions, pruritus, flushing and uriticaria

#= Palpitations, dizziness, wheeze/dyspnoea, rhinorrhoea, headache and anaphylaxis

^= Dyspepsia, nausea, vomiting, diarrhoea, constipation, abdominal pain/ cramps

NR indicates no response; PR, partial response; CR, complete response



	NR to cutaneous symptoms	PR to cutaneous symptoms	CR to cutaneous symptoms		NR to mediator symptoms	PR to mediator symptoms	CR to mediator symptoms		NR to GIT symptoms	PR to GIT symptoms	CR to GIT symptoms
Cetirizine	9	23	14		9	0	4		9	8	3
Fexofenadine	6	10	5		6	1	1		6	4	4
Monteleukast	14	4	0		14	1	0		14	3	0
Sodium Chromoglycate	1	1	0		1	0	0		1	1	5
PPI	0	0	0		0	0	0		4	16	31
Ranitidine	0	0	0		0	0	0		3	15	20