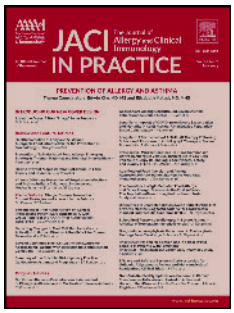

Burden of childhood cutaneous mastocytosis - severity and caregivers quality of life

Bruna Luiza Guerrer, M.D., MSc., Mariana Aparecida Pasa Morgan, M.D., MSc., Mariana Muzzolon, PhD., Lucero Noguera-Morel, PhD., Herberto Jose Chong-Neto, M.D., Ph.D., Vânia Oliveira Carvalho, M.D., Ph.D.

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Short Title: Childhood cutaneous mastocytosis and caregivers QoL

1. Bruna Luiza Guerrer. M.D., MSc. E-mail: bruna_guerrer@outlook.com. Pediatric Dermatology Division, Department of Pediatrics, Federal University of Paraná, UFPR, Curitiba, Brazil.

2. Mariana Aparecida Pasa Morgan. M.D., MSc. E-mail: mariana.morgan@hotmail.com. Ceres Faculty, Medical School of São José do Rio Preto, São José do Rio Preto, Brazil.

3. Mariana Muzzolon. PhD. E-mail: muzzolon.mariana@gmail.com. Pediatric Dermatology Division, Department of Pediatrics, Federal University of Paraná, UFPR, Curitiba, Brazil.

4. Lucero Noguera-Morel. PhD. E-mail: luceronoguera@gmail.com. Department of Dermatology, Hospital Infantil Universitario Niño Jesus, Madrid, Spain.

5. Herberto Jose Chong-Neto. M.D., Ph.D. E-mail: herberto.chong@gmail.com. Department of Pediatrics, Federal University of Paraná, UFPR, Curitiba, Brazil.

6. Vânia Oliveira Carvalho. M.D., Ph.D. E-mail: rcarvalho50@hotmail.com. Pediatric Dermatology Division, Department of Pediatrics, Federal University of Paraná, UFPR, Curitiba, Brazil.

Corresponding author: Bruna Luiza Guerrer. Address: General Carneiro Street, 181, Alto da Glória, Curitiba, Paraná, Brazil, 80060900. Telephone: #55413360-7892. E-mail: bruna_guerrer@outlook.com

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Clinical Implications

Cutaneous pediatric mastocytosis is a benign condition but pruritus and early age at symptom onset were associated with a greater impact on caregivers' quality of life, emphasizing the importance to address and mitigate this burden.

Keywords: Mastocytosis, Urticaria pigmentosa, Cutaneous mastocytosis, Child, Quality of life

Mastocytosis is a clonal mast cell disease characterized by the accumulation of these cells.[1] In children, the disease primarily affects the skin but may also involve other organs, such as the bone marrow, liver, and spleen.[2] Considered a rare disease, it shows better prognosis when it starts before two years of age.[3] Its etiology is attributed to somatic mutations in different exons of the KIT gene in mast cells.[1] The disease affects all age groups and both sexes and can be congenital.[3] The most frequent clinical presentation in children is cutaneous mastocytosis (CM), with various lesions, such as brownish to erythematous spots and plaques with positive Darier's sign.[4]

The World Health Organization (WHO) classifies CM as: maculopapular CM, diffuse CM, and mastocytoma.[2] Symptoms include pruritus, flushing, abdominal pain and diarrhea. The clinical course is variable and influenced by the age of onset, clinical classification, lesion location, severity of cutaneous manifestation, and affected organs.[5] The skin is the individual's first contact with the external environment and other people. Beyond its physical impact, mastocytosis affects the quality of life (QoL) of patients and their families.[6,7] The Family Dermatology Life Quality Index (FDLQI-BRA) is a validated tool used to measure the impact of skin diseases on caregivers' QoL[7], yet no studies have assessed the QoL of caregivers of patients with CM.

This study evaluated the clinical characteristics, severity of pediatric CM, and its impact on the QoL of caregivers. We perform an observational, analytical and cross-sectional study, with prospective data collection, included children diagnosed with CM followed at a university service from 2021 to 2023. The parameter for diagnosing CM was clinical. [2] The severity of CM was

assessed using the index SCORMA, and the QoL of caregivers using the FDLQI-BRA. The FDLQI-BRA is an instrument composed of ten multiple-choice questions. It considers physical, psychological and social aspects. Each answer scores on a Likert scale from 0 to 3, with 0 – not at all, 1 – a little, 2 – quite a lot, and 3 – very much. **Figure 1** illustrates the frequency of "not at all," "a little," "quite a lot," and "very much" answers to the 10 questions of the FDLQI-BRA. The final sum ranges from 0 to 30, with zero being the lowest impact and 30 being the highest impact on the caregiver's QoL. The SCORMA index includes the extent of affected skin, the intensity of clinical manifestations (pigmentation, erythema, vesicles, edema and Darier's sign), and the severity of subjective symptoms reported by the caregiver (triggering factors, pruritus, abdominal pain, diarrhea, bone pain and flushing). The score ranges from 0 to 100 points, and the highest score equates to higher clinical activity and disease severity.[8] The Mann-Whitney test, Fisher's exact test with Pearson's correlation model, and Pearson's chi-square test with Yates' correction were used. Considered a significance level of 5%. The study was approved by the Research Ethics Committee of the CAAE institution (23545519.3.0000.0093).

The study sample consisted of 32 pediatric patients, 20 (62.5%) of whom were male, with a median age=29 months (interquartile range [IR] = 11–60.5 months). The median age at diagnosis was 10.5 months (IR = 8.0–21.5 months). Maculopapular CM was the most frequent clinical form, present in 20 patients (62.5%), followed by mastocytoma in 10 (31.2%) and diffuse CM in 2 (6.3%). Most patients (71.9%) reported frequent symptoms such as erythema over the brown spots and pruritus (**Table I**). The severity of the disease, according to SCORMA, were significantly higher in patients with maculopapular

CM compared to those with mastocytoma ($p < 0.001$). The median FDLQI-BRA score was 7.0 (IR = 2.5–9.0) and 53.1% of caregivers experienced a very severe or severe impact on QoL (**Table I**). The impact was greater among caregivers of children with maculopapular CM compared to those with mastocytoma ($p = 0.04$). The analysis also revealed a moderate correlation ($r = 0.51$) between the FDLQI-BRA and the SCORMA, suggesting that disease severity impacts the caregivers QoL (**Figure E1,** in the Online Repository). Additionally, variables such as the presence of pruritus and age at symptom onset were identified as predictive factors of greater impact on caregivers' QoL, with these variables explaining 38% of the variability in FDLQI-BRA scores ($p < 0.001$).

This was the first study to investigate QoL in caregivers of children with CM, allowing for a better understanding of the emotional and social effects of this rare disease. There is no specific instrument to evaluate the QoL in children with mastocytosis, although the Mastocytosis QoL has been validated for adults.[9] Heinze et al. assessed QoL using the Children's Dermatology Life Quality Index (CDLQI) in 43 children with mastocytosis, and cutaneous pruritus, intimidation, teasing, and embarrassment regarding skin appearance have been reported. The median score suggested that CM mildly impacts children's QoL; however, this instrument was developed to assess QoL in children with eczema.[10] The impact on the QoL of caregivers of patients with mastocytosis has been ignored.[7] By employing the FDLQI-BRA, a significant impact was observed, especially among those with the maculopapular form, which may be related to the extent of the disease and the frequency of symptoms. Caregivers of children with itching and those who had earlier symptom onset had a greater

impact on their QoL. This suggests that the duration of symptoms experienced and the intensity of clinical manifestations have a substantial effect on the emotional and social well-being of caregivers.

Regarding clinical manifestations, CM was more frequent in males, with the maculopapular form being the most prevalent, followed by mastocytoma. The most common symptoms were pruritus and erythema on brownish spots, findings that are consistent with previous studies.[4] Blisters and flushing were more frequent in mastocytomas, possibly due to their larger size and location in areas of friction. No sign or symptom was correlated with other co-existing conditions. This study has the limitation of the small sample size; however, we emphasize the need to focus not only on the clinical treatment of mastocytosis but also on the psychological and social support for caregivers. In conclusion, this study demonstrates that although CM has a good prognosis, its impact on caregivers' QoL is considerable and should be taken into account in clinical management and the overall approach to pediatric patients.

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207 **Figure 1.** Classification of the quality of life of families of patients with
208 cutaneous mastocytosis and predictors of the quality of life score.

209

Table I. Frequency of signs and symptoms and responses to the Family Dermatology Life Quality Index, classification of the quality of life of families of patients with cutaneous mastocytosis.

Frequency of signs and symptoms

Symptoms and signs	Total N (%)	Maculopapular CM (N = 20)	Mastocytoma (N = 10)	p Value[a]
Presence of symptoms	25 (78.1%)[b]	16 (80.0%)	8 (80.0%)	1.00
Erythema over the brownish macules	23 (71.9%)[b]	15 (75.0%)	7 (70.0%)	1.00
Pruritus	19 (59.4%)[b]	15 (75.0%)	3 (30.0%)	**0.04**
Bullae/vesicles	9 (28.1%)[b]	4 (20.0%)	4 (40.0%)	0.38
Osteoarticular pain	6 (18.7%)	4 (20.0%)	2 (20.0%)	1.00
Flushing	5 (15.6%)	1 (5.0%)	4 (40.0%)	**0.03**
Abdominal pain	2 (6.2%)	2 (10.0%)	0 (0.0%)	0.54
Diarrhea	2 (6.2%)	1 (5.0%)	1 (10.0%)	1.00

Classification of quality of life by FDLQI-BRA	N (%)
No effect	3 (9.4%)
Mild	10 (31.2%)
Moderate	2 (6.2%)
Severe	11 (34.4%)
Very severe	6 (18.7%)

[a]p Values of <0.05 were considered as statistically significant.
[b]The two cases of diffuse CM, only one reported erythema, pruritus, and formation of vesicles/bullae.
FDLQI-BRA – Brazilian Version of the Family Dermatology Life Quality Index; CM – Cutaneous Mastocytosis