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1 **Criteria for the regression of pediatric mastocytosis: a long-term follow-up**

2

3 Laura Polivka, MD-MSc^{1-3*}, Julien Rossignol, MD-PhD^{2-4*}, Antoine Neuraz, MD-MSc⁵,

4 Djiba Condé, MSc¹, Julie Agopian, MSc^{3,6,7}, Cécile Méni, MD¹, Nicolas Garcelon, MD-PhD⁵,

5 Patrice Dubreuil, PhD^{3,6}, Leïla Maouche-Chrétien, PhD², Smail Hadj-Rabia, MD-PhD¹,

6 Olivier Hermine, MD-PhD^{2-4*}, Christine Bodemer, MD-PhD^{1*}

7 *Equal contribution

8

9 1. Department of Dermatology, Reference Center for Genodermatoses (MAGEC), Necker-
10 Enfants Malades Hospital (AP-HP5), Paris-Centre University, Imagine Institute, INSERM
11 U1163, Paris, France.

12 2. Laboratory of Molecular Mechanisms of Hematologic Disorders and Therapeutic
13 Implications, Necker Branch, INSERM U1163 and CNRS ERL 8654, Necker-Enfants
14 Malades Hospital (AP-HP), Paris-Centre University, Imagine Institute, Paris, France.

15 3. CEREMAST, Imagine Institute, INSERM U1163, Paris, France.

16 4. Department of Hematology, Necker-Enfants Malades Hospital (AP-HP5), Paris-Centre
17 University, Imagine Institute, Paris, France.

18 5. Department of Bioinformatics, Necker Branch, Necker-Enfants Malades Hospital (AP-
19 HP5), Paris-Centre University, Imagine Institute, INSERM U1163, Paris, France.

20 6. Centre de Recherche en Cancérologie de Marseille, équipe Labellisée Ligue nationale
21 contre le Cancer, INSERM U1068, Marseille, France.

22 7. Association Française pour les Initiatives de Recherche sur le Mastocyte et les
23 Mastocytoses (AFIRMM), France.

24

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26 group

27

28 **Corresponding authors:**

29 Christine Bodemer, Department of Dermatology and Referral Center for Genodermatoses
30 (MAGEC), Imagine Institute, Necker-Enfants Malades Hospital, APHP5 and Paris Centre
31 University, 149 rue de Sèvres, F-75743 Paris cedex 15, France. christine.bodemer@aphp.fr;
32 tel.: +33-144-494-672; fax: +33-144-494-660

33 and

34 Laura Polivka, Imagine Institute, INSERM U1163, 24 boulevard Montparnasse, F-75015
35 Paris, France. laura.polivka@institutimagine.org; tel.: +33-142-754-278; fax: +33-142-754-

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46

47 **Abstract**

48 **Background.** Mastocytosis is a neoplastic condition characterized by the accumulation of
49 mast cells (MCs) in one or more organs. Adults tend to have persistent, systemic mastocytosis
50 (SM), whereas MC infiltration in children is usually limited to the skin and typically regresses
51 after several years. Both adults and children could display MC activation symptoms (MCAs)
52 due to MC mediator release. In more than 85% of both adult and pediatric cases, *KIT*
53 mutations are present, the *KIT* D816V mutation being present in most affected adults but in
54 only half of affected children.

55 **Objective.** To identify the clinical, biological and molecular factors associated with the
56 regression of cutaneous mastocytosis (CM) in children, and to assess the correlation between
57 MCAs and CM regression.

58 **Methods.** Patients having suffered from pediatric-onset mastocytosis for at least 8 years were
59 included in a longitudinal cohort study. Clinical data, the baseline serum tryptase level, the
60 *KIT* sequence, and the progression of MCAs and CM were recorded.

61 **Results.** CM regressed in 210 of the 272 included patients (77.2%; mean time to regression:
62 6.10 years). The rare cases of aggressive SM were symptomatic from the outset. Congenital
63 mastocytosis and the *KIT* D816V mutation were associated with CM regression [odds
64 ratio=0.48 (p=0.031) and 0.173 (p=0.031), respectively]. Aggravation of MCAs over time
65 was correlated with the persistence of skin lesions. However, the MCAs became more intense
66 in 19% of the patients with MCAs at baseline and CM regression - justifying long-term
67 follow-up in this setting.

68 **Conclusion.** Our results open up new hypotheses with regard to the spontaneous regression of
69 CM in pediatric patients.

70 **Highlights box**

71

72 **1. What is already known about this topic?**

73

74 In contrast to adult-onset mastocytosis, mast cell infiltration in children is usually limited to
75 the skin and typically regresses after several years. The underlying mechanisms have not been
76 yet been identified.

77

78 **2. What does this article add to our knowledge?**

79

80 In children, congenital disease and the *KIT* D816V mutation were associated with the
81 regression of cutaneous mastocytosis. Symptoms of mast cell activation may worsen over
82 time - even after cutaneous regression. The rare aggressive forms were symptomatic from the
83 outset.

84

85

86 **3. How does this study impact current management guidelines?**

87

88 *KIT* D816V is not associated with a poor prognosis factor in children. Long-term follow-up is
89 mandatory for children with mastocytosis and symptoms of mast cell activation.

90

91

92 **Keywords**

93 Childhood mastocytosis – cutaneous mastocytosis – mast cell - mast cell activation symptom
94 – *KIT* mutation – tryptase – prognosis

95

96 **Abbreviations**

97 ASM: aggressive systemic mastocytosis

98 CI: 95% confidence interval

99 CM: cutaneous mastocytosis

100 DCM: diffuse cutaneous mastocytosis

101 MC: mast cell

102 MCAs: mast cell activation symptoms

103 MPCM: maculopapular cutaneous mastocytosis

104 OR: odds ratio

105 SM: systemic mastocytosis

106 WHO: World Health Organization

107 WT: wild type

108

109 **Introduction**

110 Mastocytosis corresponds to a heterogeneous group of neoplastic conditions characterized
111 by the expansion and accumulation of mast cells (MCs) in one or more organs (such as the
112 skin, bone marrow, spleen, lymph nodes, and gastrointestinal tract).¹⁻³ Disease can appear in
113 childhood or in adulthood. Pediatric patients generally exhibit cutaneous mastocytosis (CM),
114 in which MC infiltrates are limited to the skin and the resulting skin lesions spontaneously
115 recede after several years in most patients.⁴⁻¹⁰ Congenital mastocytosis is defined by the
116 presence of lesions at birth. The clinical manifestations of mastocytosis are related to the
117 clonal accumulation of MCs (depending on which tissues are involved) and the effects of
118 mediators released from the MCs. In fact, over 200 mediators with a role in various
119 physiological and pathological conditions have been identified in MC granules, including
120 heparin and proteases like tryptase and chymase.¹¹ As in cases of adult-onset mastocytosis,
121 most of cases of pediatric mastocytosis present symptoms of mast cell activation (MCAs, due
122 to MC mediator release), in addition to skin involvement.^{12,13} Somatic gain-of-function
123 mutations in the *KIT* gene are found in most of patients with mastocytosis. In adult-onset
124 mastocytosis (which is usually persistent and systemic), the *KIT* D816V mutation (in exon 17)
125 is the most frequent, and is detected in more than 85% of cases.^{14,15} In contrast, a mutation in
126 exon 17 is found in only 43% of pediatric cases - the same prevalence as for mutations
127 affecting exons 8, 9, 10 or 11.^{16,17} Although it has been hypothesized that the mutational
128 differences observed between pediatric and adult cases explain (at least in part) the regression
129 of CM, the underlying mechanisms have not been yet identified.^{3,18,19} Nevertheless, a number
130 of clinical factors appeared to be associated with spontaneous disease improvement; they
131 include early disease onset (within 12 months of birth) and the type of lesion (e.g.
132 maculopapular cutaneous mastocytosis (MPCM) with large lesions).^{17,20}

133 The often prominent, severe worsening of MCAs can significantly impact the patient's quality
134 of life and can sometimes trigger life-threatening complications; however, the relationship
135 between the regression of MCAs and the regression of skin lesions in pediatric-onset
136 mastocytosis has not been clearly elucidated.

137 The objective of the present retrospective study of the largest yet cohort of well-characterized
138 patients with pediatric-onset mastocytosis and at least 8 years of follow-up were to (i)
139 identify the clinical, biological and molecular factors associated with spontaneous CM
140 regression in children, and (ii) to analyze the correlation between MCA symptoms and the
141 skin lesion regression.

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146 **Material and Methods**

147 **Study population**

148 We performed a retrospective study in the dermatology department at Necker Children's
149 Hospital (Paris, France), which coordinates the pediatric branch of the CEREMAST national
150 reference center for mastocytosis. This was an observational study; laboratory tests (*KIT* gene
151 sequencing and blood chemistry tests) were performed only after the patient's parents had
152 been given a comprehensive explanation and had given their consent (see below).
153 Accordingly, all patients with pediatric-onset mastocytosis who had consulted or been
154 hospitalized between January 1st, 1996, and December 31st, 2018, were considered for
155 eligibility in the study (Figure 1). Mastocytosis was defined and classified according to the
156 World Health Organization (WHO) criteria (see Supplemental Methods). In most cases, the
157 diagnosis of CM was based solely on clear clinical signs (major criteria); for ethical reasons, a
158 skin biopsy (to screen for minor criteria) was not performed. Patients were selected from the
159 CEREMAST national cohort, which was set up as part of a physiopathological study of
160 mastocytosis in which information is stored in electronic medical records. The study protocol
161 was approved by the local investigational review board (CPPRB Groupe Hospitalier de Paris
162 Necker", Paris, France, n°03-01-05; July 7th,2003). Regardless of the type of mastocytosis,
163 *KIT* sequencing of a skin biopsy was always suggested if it was likely to improve the patient's
164 care. The information extracted from the CEREMAST was supplemented with information
165 from Necker Children's Hospital's data warehouse, which integrates free text data
166 (hospitalization, consultation and prescription reports, etc.) and coded data (laboratory
167 results).²¹ The data warehouse was queried with the following diagnostic codes:
168 "mastocytosis", "cutaneous mastocytosis", "diffuse cutaneous mastocytosis", "mastocytoma",
169 and "urticaria pigmentosum". We next analyzed the characteristics of individual patients by
170 referring to their electronic medical records; erroneous diagnoses, cases of adult-onset

171 mastocytosis, and cases of mastocytosis diagnosed less than 8 years previously were all
172 excluded. Hence, all the included patients presented with confirmed pediatric-onset
173 mastocytosis diagnosed at least 8 years previously. We analyzed the patient's electronic and
174 paper-based medical records, and pictures of their skin.

175 **Patient selection.** Between January 1st, 1996, and December 31st, 2018, a total of 687 patients
176 consulted for pediatric-onset mastocytosis at the French National Reference Center. Seventy-
177 seven patients were excluded because of an incorrect diagnosis. Overall, 272 of the remaining
178 610 patients had suffered from pediatric-onset mastocytosis for at least 8 years, and so were
179 selected for long-term follow-up (Figure 1). Twelve patients were lost to follow-up (the
180 changes in CM and MCAs were not documented) and so were excluded from analyses of the
181 regression of CM and MCAs.

182 **Data collection.** The study variables were assessed twice: at disease onset (during a
183 consultation) and at a study visit (a 'phone interview' or a clinical examination) by
184 dermatologists from the same department at the CEREMAST, using an electronic case report
185 form. For all identified patients, the following items of data were collected: sex; age at onset;
186 age at diagnosis; family history of mastocytosis; the type of cutaneous mastocytosis (MPCM,
187 mastocytoma, or diffuse cutaneous mastocytosis (DCM)), the presence of one or more of the
188 suggested symptoms of MCA: pruritus, flushes, urticaria, diarrhea, abdominal pain, epigastric
189 pain, food reactions, anorexia, nausea, vomiting, loss of consciousness, hypotension, episodes
190 of pallor, a drained feeling, asthenia, headaches, nightmares, sleep disorders, dyspnea,
191 muscle/joint/bone pain, palpitations, polyuria, emotional disturbance or behavioral disorders,
192 the baseline serum tryptase level, *KIT* gene sequencing data, and the change over time in
193 MCAs and skin lesions. Cases of MPCM were subdivided in three groups: MPCM-large
194 subgroup [patients with at least one large (>1 cm) or polymorphic lesion]; MPCM-small
195 subgroup [patients with small (<5 mm) lesions] and non-classified MPCM (patients for whom

196 the size of the lesions was not known). Congenital mastocytosis was defined by the presence
197 of lesions at birth. The change over time in skin lesions was classified as complete regression
198 (i.e. the healing of lesions, with the absence of Darier's sign), partial regression (a decrease in
199 the number of lesions, and/or lightening of the lesions), or stabilization. The presence or
200 absence of the 26 above-mentioned MCAs was rated (with one point for each symptom) at
201 baseline and at last follow-up. The change over time in MCAs was classified as complete
202 regression, partial regression (a decrease of at least one point), stabilization, or aggravation
203 (an increase of at least one point).

204 **Screening for *KIT* mutations**

205 A skin biopsy was collected in 66 of 272 enrolled patient for *KIT* mutation analysis using a
206 highly sensitive technique (described in the Supplemental Methods) but only if the patient's
207 parents or legal guardian had given his/her informed consent for genetic screening or if the
208 patient had systemic mastocytosis (SM) requiring specific treatment. A bone marrow biopsy
209 with *KIT* sequencing was performed only in patients (n=7) with signs suggestive of systemic
210 mastocytosis (cytopenia, organomegaly, malabsorption syndrome and bone damage). Three
211 categories of *KIT* mutation were defined: a point mutation at codon 816, a mutation outside
212 codon 816, and the wild type (WT).

213 **Statistical analyses** are described in the Supplemental Methods.

214 **Results**

215 **Characteristics of the study population**

216 The main characteristics of the study population (n=272) are summarized in Table 1. The
217 male-to-female ratio was 1.23, 115 patients (42.3%) had congenital mastocytosis. Twenty-
218 three patients (8.5%) had familial mastocytosis (i.e. at least one first-degree parent with
219 mastocytosis). The mean (range) disease duration at the end of our study was 12.93 years
220 (8.1–31.7). We observed 211 (77.6%) patients with MPCM, 46 (16.9%) with mastocytoma,
221 and 15 (5.5%) with DCM. The frequency of congenital forms was higher among patients with
222 mastocytoma (54.3%) or DCM (53.3%) than among patients with MPCM (38.9%), although
223 the intergroup differences were not statistically significant (p=0.069 and p=0.29,
224 respectively). One hundred and ninety-five patients (71.7%) presented with MCAs at
225 diagnosis, with a mean (range) of 2.04 signs (1–11). There were no significant differences
226 between the MPCM, mastocytoma, and DCM groups with regard to the number of MCAs at
227 baseline, except that cutaneous signs of MCA (pruritus and/or flushes) were significantly
228 more frequent in the DCM group (73.3%) than in the MPCM group (40.8%; p=0.016, Table 2
229 and Figure E1). The *KIT* gene was sequenced (using a skin biopsy sample) in 66 of the 272
230 patients (24.3%): 28 of these 66 (42.4%) carried a mutation in codon 816 (exon 17), 28
231 (42.4%) carried a *KIT* mutation outside codon 816, and 10 (15.2%) had a WT *KIT* gene. Fifty
232 of the 66 patients have already been described by Bodemer et al.¹⁶ The different types of *KIT*
233 mutation are shown in Table E1. No genotype-phenotype correlations were apparent (data not
234 shown). The mean serum tryptase level at baseline was 7.52 $\mu\text{g.L}^{-1}$ [1–60] in the 121 assayed
235 patients. As expected, the mean (range) tryptase level was significantly higher in the DCM
236 group [23.99 (2-60) $\mu\text{g.L}^{-1}$] than in the MPCM group [7.36 (1 - 45.2) $\mu\text{g.L}^{-1}$; p<0.0001] and
237 significantly higher in the MPCM group than in the mastocytoma group [4.32 $\mu\text{g.L}^{-1}$, (1.3–
238 11.5), p=0.045] (Figure E1). Apart from the tryptase level, the MPCM, mastocytoma and

239 DCM groups did not differ significantly (data not shown) with regard to the main
240 characteristics summarized in Table 1.

241 Within the MPCM group, 85 patients (40.3%) had large MPCM lesions, 78 (37%) had small
242 MPCM lesions and 48 patients (22.7%) had non-classified MPCM lesions. The frequency of
243 familial mastocytosis was significantly higher in the MPCM-small subgroup (17.9%) than in
244 the MPCM-large subgroup (5.9%, $p=0.026$), whereas the frequency of congenital
245 mastocytosis was higher in the MPCM-large group (48.2% vs. 37.5%, $p=0.016$). Disease
246 onset after the age of 2 was recorded for 19 patients, all of whom belonged to the MPCM-
247 small or –non-classified subgroups. The groups did not differ significantly with regard to the
248 distribution of the *KIT* mutations (Table 1). The characteristics of the included participants
249 and the screened (source) population were similar ($n=610$, Table E2). Five of the 610 patients
250 in the source population presented with SM (as defined by the WHO criteria): three of these
251 five had *KIT*-D816V-positive, congenital, aggressive systemic mastocytosis (ASM) from the
252 onset, with DCM and MC infiltration of the bone marrow, liver, spleen and digestive tract; the
253 remaining two developed acute myeloid leukemia in which a $t(8;21)$ or $(1;17)$ translocation
254 was associated with a *KIT* D816V or N822Y mutation, respectively (Table E3).¹

255 The main differences between patients for whom mastocytosis was congenital or appeared
256 within one month of birth (the congenital group) and those for whom mastocytosis appeared
257 later than a month after birth (the non-congenital group) are summarized in Table 3. We
258 found that MPCM was significantly more common in the non-congenital group (83.4%) than
259 in the congenital group (70.9%, $p=0.019$). Mastocytoma and DCM were more common (but
260 not significantly) in the congenital group. The distribution of *KIT* mutations (notably the
261 frequency of *KIT* point mutations in codon 816) was similar in the two groups (Figure E2).
262 The distribution of the *KIT* mutations as a function of age of onset is shown in Figure E2.

263 **Changes over time in CM**

264 Two hundred and ten of the 260 patients (80.8%) showed complete (n=18) or partial (n=192)
265 regression of CM at last follow-up (Figure E3). The mean (range) time to regression was 6.1
266 years (1.48-21.9). Forty-one patients were stable at the last examination, and 9 patients had a
267 greater number of lesions (i.e. worsening). The clinical, biological and molecular variables
268 associated with changes in CM are summarized in Table 4. Congenital mastocytosis was
269 associated with CM regression (odds ratio (OR)=0.476, 95% confidence interval
270 (CI)=[0.236–0.917], p=0.031). The presence of one or more MCAs at baseline was a
271 significant prognostic factor for CM progression (OR=2.20, 95%CI=[1.05 – 5.06], p=0.047).
272 However, each individual MCAs (digestive symptoms, pain, a drained feeling etc.) was not
273 significantly associated with changes over time in CM (data not shown), except for the
274 presence of pruritus or flushes at baseline; surprisingly, these were associated with CM
275 regression (OR=0.19, 95%CI=[0.072–0.43], p=0.000; and OR=0.3, 95%CI=[0.128 – 0.663],
276 p=0.004, respectively). Aggravation or stabilization of MCAs was significantly correlated
277 with worsening CM (OR=3.36, 95%CI=[1.28 – 9.13], p=0.015). Sex, familial mastocytosis,
278 the type of CM, the different types of MPCM and the serum tryptase level at baseline were
279 not significantly associated with the disease outcome.

280 The presence of a *KIT* point mutation in codon 816 was significantly associated with CM
281 regression (OR=0.173, 95%CI=[0.025–0.719], p=0.031). In contrast, a WT *KIT* genotype was
282 associated (albeit not significantly) with the aggravation of skin lesions (OR=3,
283 95%CI=[0.666–12.6], p=0.135). Of the 50 stable (n=41) or worsening (n=9) patients, 14
284 patients (12 stable and 2 worsening) had *KIT* sequence data: two patients presented with a
285 *KIT* point mutation at codon 816, eight patients presented with other *KIT* mutations, and four
286 patients were WT (notably two patients with worsening). Two patients developed
287 extracutaneous disease features. A *KIT* D816V+patient in the MPCM-small subgroup with
288 MCAs from the age of 1 developed a small but painful osteolytic bone lesion with MC

289 infiltrates at puberty but did not meet the criteria for ASM. Another *KIT* D816Y+ patient with
290 MPCM-large congenital mastocytosis developed hepatomegaly. No liver biopsies were
291 performed. In both cases, a bone marrow aspirate confirmed the presence of MC infiltrates.
292 None of the 272 included patients had developed ASM.

293 **Changes over time in MCA symptoms**

294 Seventy-seven patients (29.6%) were free of MCAs throughout the study. Of the remaining
295 183 patients, 144 (78.7%) showed complete (n=85) or partial (n=59) regression of the MCAs.
296 Twenty-two (12%) patients were classified as stable at the last examination, and the number
297 of MCAs increased in 17 (9.3%) patients (i.e. worsening). The clinical, biological and
298 molecular markers associated with an increase in the number of MCAs are summarized in
299 Table 5. The number of MCAs (and especially the presence of urticaria) at baseline was a
300 prognostic factor for the worsening of MCAs (OR=653, 95%CI=[1.18.10²-1.24.10⁴], p=0.000
301 and OR=4.97, 95%CI=[1.05-26.2], p=0.041, respectively). Taken individually, the other types
302 of MCAs (digestive symptoms, pain, a drained feeling etc.) were not significantly associated
303 with worsening of MCAs (data not shown). Likewise, sex, congenital mastocytosis, familial
304 mastocytosis, the type of CM, the different types of MPCM and the type of *KIT* mutation
305 were not significantly associated with the course of the MCAs. The serum tryptase level at
306 baseline was not significantly associated with the course of the MCAs (OR=1.05,
307 95%CI=[0.973 – 1.17], p=0.341). In a multivariate analysis, however, a *KIT* point mutation in
308 exon 816 became significantly associated with the regression of MCAs (Table E4).

309 **The correlation between changes in MCAs and CM**

310 Aggravation/stability of MCAs was significantly correlated with worsening/stability of CM
311 (OR=3.36, p=0.015). However, baseline MCAs persisted or even worsened in 27 patients
312 with a favorable CM outcome (Figure 2). The regression of both MCA symptoms and CM was
313 associated with the number of MCAs at baseline and the presence of cutaneous symptoms

314 (pruritus and flushing), relative to patients not showing this correlation (OR=2.5 and 1.97,
315 respectively, $p=0.0002$, Table 6).

316 **Cluster analysis of the different MCAs at diagnosis and changes in CM/MCAs**

317 A cluster analysis of the different MCAs identified four clusters of patients (Figure E4).
318 Clinically, cluster 1 was characterized by isolated food intolerance, cluster 2 was not highly
319 specific, cluster 3 was characterized mainly by flushes and pruritus, fatigue with a drained
320 feeling, abdominal pain and intestinal transit disorders, and cluster 4 was characterized by
321 pruritus (but not flushes), abdominal pain, and intestinal transit disorders. The changes over
322 time in each group are depicted in Figure E4. There were no significant intergroup differences
323 with regard to changes over time in CM. Patients in cluster 3 were significantly more likely to
324 experience a decrease in MCAs outcome than patients in cluster 1 (taken as a reference) were
325 ($p=0.008$, Figure E4). The same association was seen for cluster 4 but was not statistically
326 significant ($p=0.08$).

327

328 **Discussion:**

329 Here, we analyzed a large cohort of patients with pediatric-onset mastocytosis (n=610)
330 and defined prognostic factors in 260 patients with at least 8 years of follow-up (mean
331 duration of disease: 12.93 years). We showed that a spontaneous CM regression was
332 significantly associated with not only congenital disease but also (unexpectedly) a *KIT*
333 D816V mutation. Moreover, even though the worsening of MCAs was correlated with the
334 worsening of CM, MCAs continued to worsen into adulthood in a subset of patients with CM
335 regression. Sex and familial mastocytosis were not associated with changes in CM.

336 The demographic characteristics of our study population were similar to those reported
337 in the literature, namely slight male predominance (male/female ratio: 1.23), disease onset
338 early in life (mean age at onset: 301.2 days), a relatively high frequency of congenital forms
339 (42.3%), a predominance of MPCM (77.6%) relative to mastocytoma (16.9 %) and DCM
340 (5.5%), and a mean time to CM regression of 6.1 years (Table 1).⁴ Although aggressive forms
341 of SM were rare (n=5 out of 610, 0.82%), the fact that they were always clinically apparent at
342 disease onset meant that we did not systematically have to obtain bone marrow aspirates in
343 children lacking obvious clinical signs of ASM (organomegaly with impaired organ function,
344 pancytopenia, etc.).

345 As expected, a large minority (42.4%) of the patients presented with a *KIT* point mutation in
346 codon 816.¹⁶ The present report is the first to show that this mutation is (like congenital CM)
347 significantly associated with CM regression (OR=0.173, p=0.031, Table 4) in pediatric-onset
348 mastocytosis; however, in this study we confirmed the presence of the *KIT* D816V mutation
349 in only 28 patients. In contrast, the *KIT* D816V mutation is associated with disease
350 persistence in adult forms of mastocytosis.²² In our study, mutations outside codon 816 did
351 not appear to be significantly associated with the change over time in CM; this was probably
352 because the follow-up period was too short.

353

354 We did not find a *KIT* mutation in two patients with worsened of cutaneous lesions. As in
355 adult forms of ASM, the absence of a *KIT* mutation suggests the causal presence of one of
356 more other gene mutations. In the present study, the absence of a *KIT* mutation appeared to be
357 associated with the worsening of CM (OR=3.0, 95%CI=[0.666 – 12.6], p=0.135, Table 4).²³
358 The distribution of the *KIT* mutations (notably the *KIT* point mutation in codon 816) was
359 similar in congenital and non-congenital forms of mastocytosis (Figure E2). Thus, the
360 mutational differences between children and adults with mastocytosis (especially the high
361 prevalence of *KIT* D816V mutation in adults) cannot alone explain the outcome of CM. Based
362 on Gentek et al.'s research on the ontogeny of MCs, we propose a new hypothesis for the
363 regression of pediatric-onset mastocytosis.²⁴ Gentek et al. showed that in the embryonic
364 mouse, MCs have two hematopoietic origins: the yolk sac and the bone marrow. The two MC
365 lineages differ with regard to the phenotype and the gene expression pattern. Interestingly,
366 embryonic skin MCs derived from the yolk sac persist after birth and are then gradually
367 replaced by the definitive adult MCs. We therefore hypothesized that regardless of the nature
368 of the *KIT* gene mutation, mastocytosis will regress over time if the mutation occurs in
369 senescent yolk-sac MCs. Here, we did not find a correlation between the *KIT* genotype and
370 the patient phenotype; hence, the *KIT* mutation alone does not explain the heterogeneous
371 symptoms observed in all the various kinds of mastocytosis. This observation strongly
372 suggests that one or more mutations in one or several genes are involved - perhaps in synergy
373 with a *KIT* mutation - in the development of mastocytosis.^{25,26} The association between *KIT*
374 mutation and regression may be related to the presence of other beneficial factors such as an
375 increase over time in the expression of MC-inhibiting chondroitin or heparan sulfate.²⁷

376

377 The aggravation of MCAs was significantly correlated with the worsening of CM (OR=3.36,
378 p=0.015, Table 4). Interestingly, MCAs persisted or even worsened in 27 of the 142 patients
379 (19%) with these symptoms at baseline and a favorable CM outcome (Figure 2) - suggesting
380 that long-term follow-up of these patients might nevertheless be necessary. Thus, we
381 identified two subgroups of patients with CM regression: (i) those in whom both CM and
382 MCAs regressed (n=115), and (ii) those in whom CM regressed despite the worsening or
383 persistence of MCAs (n=27, subgroup 2). The only significant differences between these two
384 groups were the number of MCAs at baseline and the presence of skin symptoms (pruritus and
385 flushing). Surprisingly, pruritus and flushing were more frequent in the “CM and MCA
386 regression” subgroup than in the other subgroup (number of MCAs: 2.5 and 1.97 respectively,
387 p=0.0002, Table 6) - probably because these symptom;s are more strongly associated with the
388 abnormally high MC count than with MC activation *per se*. The difference between these groups
389 might be related to the presence of mutations or polymorphisms in one or more of the genes
390 involved in MCA; however, addressing this question would require an extensive molecular
391 investigations. The evolution of the levels of serum tryptase, and urinary n-methyl-histamine,
392 urinary 2,3-dinor-11 β -prostaglandin F_{2 α} , and urinary leukotriene E4 in this patient population
393 might provide further insights.

394 The present study is the first to have reported on such a large number of cases and to have
395 specified the various MCAs and their changes over time. Symptoms of MCA were frequent in
396 patients with CM (71.7%) and appeared not to be related to the extent of skin involvement
397 (except for pruritus and flushing, Table 2 and Figure E1). Thus, the type and the number of
398 MCAs appear to be more strongly related to a qualitative defect in diseased MCs than to the
399 high MC count *per se*. Of all the individual MCAs, only the presence of urticaria at diagnosis
400 was significantly associated with a worsening of MCAs in general. At present, clinicians lack
401 a validated scoring system for the qualitative and quantitative evaluation MCAs in children.

402 The development of this type of score might improve patient management in general and the
403 assessment of drug efficacy in particular.

404 Our cluster analysis of the MCAs at baseline identified between four clusters of patients
405 (Figure E4). In two clusters (patients presenting with pruritus and flushes at baseline or
406 pruritus without flushes at baseline, respectively), the MCAs decreased over time. These
407 findings will have to be validated in a study with greater statistical power.

408 Although our sample size was large for a rare disease, the study's retrospective design, and
409 the low percentage of patients with *KIT* gene sequence data constituted limitations.

410 **Conclusion**

411 In a retrospective study of the largest yet cohort of well-characterized patients with pediatric-
412 onset mastocytosis and at least 8 years of follow-up by the same clinicians, we showed that
413 congenital mastocytosis and the *KIT* D816V mutation were associated with spontaneous CM
414 regression. Furthermore, even though the worsening of MCAs was correlated with the
415 worsening of CM, we found that MCAs continued to worsen into adulthood in a subset of
416 patients with CM regression. The latter observation suggests that several different
417 mechanisms are involved in the accumulation and the activation of MCs and justifies long-
418 term follow-up in these pediatric patients with CM regression.

419

420

421

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512 **Table and figure legends**

513 **Table 1.** Main characteristics of the study population and the different cutaneous
514 mastocytosis subtype groups.

515 DCM: diffuse cutaneous mastocytosis, F: female, M: male, MCAs: mast cell activation
516 symptoms, MPCM: maculopapular cutaneous mastocytosis, NC: non-classified.

517 * $p < .05$

518 **Table 2.** Main mast cell activation symptoms at baseline, as a function of the type of
519 cutaneous mastocytosis

520 DCM: diffuse cutaneous mastocytosis, MPCM: maculopapular cutaneous mastocytosis.

521 * $p < .05$

522 **Table 3.** Congenital vs. non-congenital mastocytosis

523 DCM: diffuse cutaneous mastocytosis, F: female, M: male, MPCM: maculopapular cutaneous
524 mastocytosis, NC: non-classified.

525 * $p < .05$

526 **Table 4.** Univariate analysis – clinical, biological and molecular variables associated with the
527 progression of cutaneous mastocytosis

528 MCAs: mast cell activation symptoms, MPCM: maculopapular cutaneous mastocytosis.

529 * $p < .05$, ** $p < .01$, *** $p < .001$

530 ¹ Other types of MCAs (digestive symptoms, pain, a drained feeling etc.) were not
531 significantly associated with changes in CM (data not shown)

532 **Table 5.** Univariate analysis – clinical, biological and molecular variables associated with the
533 progression of MCAs.

534 CM: cutaneous mastocytosis, MCAs: mast cell activation symptoms, MPCM: maculopapular
535 cutaneous mastocytosis.

536 * $p < .05$, *** $p < .001$

537 ¹ Other types of MCAs (digestive symptoms, pain, a drained feeling etc.) were not
538 significantly associated with the overall progression of MCAs (data not shown)

539 **Table 6.** A comparison of clinical, biological and molecular variables in patient group 1
540 (correlated regression of both CM and MCAs) and patient group 2 (no correlation).

541 CM: cutaneous mastocytosis, DCM: diffuse cutaneous mastocytosis, F: female, M: male,
542 MCAs: mast cell activation symptoms, NC: non-classified.

543 *p<.05, ***p<.001

544

545 **Figure 1.** Study flow chart

546 **Figure 2.** Correlation between CM regression and changes over time in MCAs.

547 CM: cutaneous mastocytosis, MCAs: mast cell activation symptoms, MPCM: maculopapular
548 cutaneous mastocytosis.

549

550

Figure 1. Study flow chart

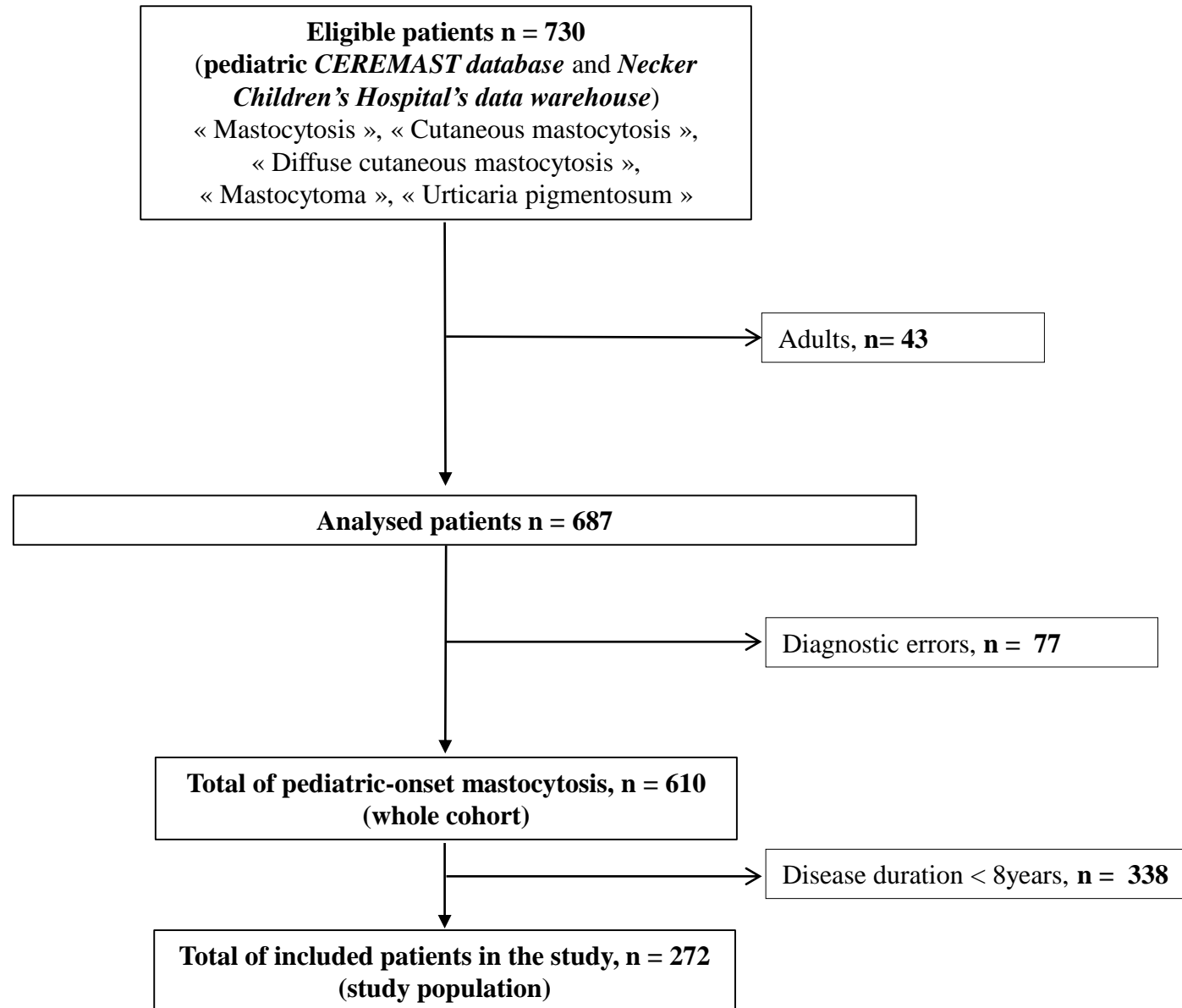
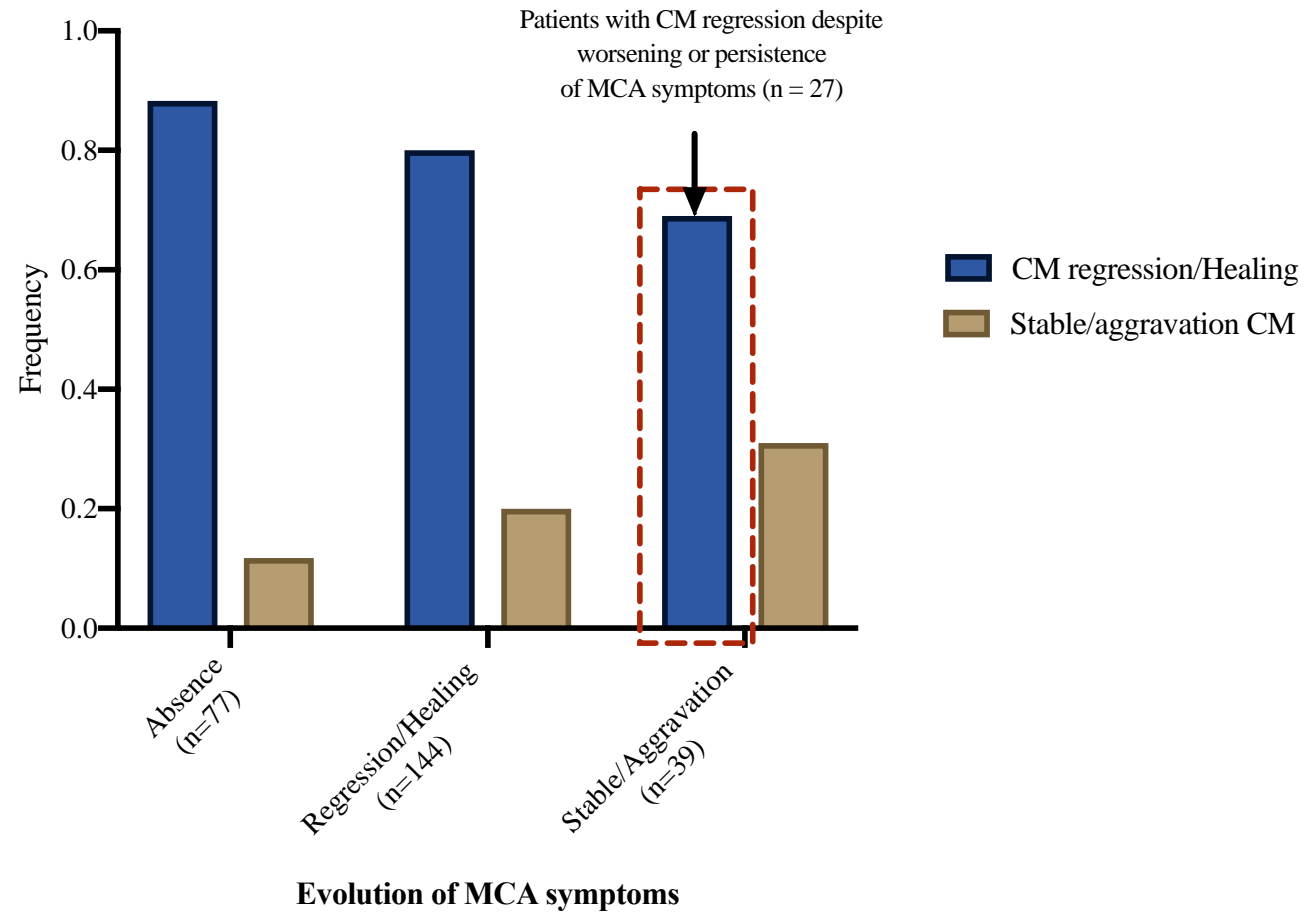


Figure 2. Correlation between CM regression and changes over time in MCAs



For 12 patients, cutaneous and MCA symptoms evolutions were unknown (patients lost to follow-up)

Table 1. Main characteristics of the study population and the different cutaneous mastocytosis subtype groups

Characteristics	Population n = 272 (n/total%)	MPCM n = 211 (n/total%)	MPCM- large n = 85	MPCM- small n = 78	p.value (MPCM- large vs MPCM- small)	MPCM- NC n = 48	Mastocytoma n = 46 (n/total%)	DCM n = 15 (n/total%)
Clinical								
Females	122	93	37	36	-	20	22	7
Males	150	118	48	42	-	28	24	8
Sex ratio (M/F)	1.23	1.27	1.43	1.17	0.75	1.4	1.09	1.14
Mean age at diagnosis (days)	1308.5	1319	1369.3	1348.6	-	1184.5	1263,2	1302
Mean age at onset (days)	301.23	302.22	305.93	302.22	-	305.05	300,87	329,82
Congenital	115 (42.3)	82 (38.9)	41 (48.2)	23 (29.5)	0.016*	18 (37.5)	25 (54.3)	8 (53.3)
Familial mastocytosis	23 (8.5)	22 (10.4)	5 (5.9)	14 (17.9)	0.026*	3 (6.25)	1 (2.2)	0 (0)
Number of MCAs at diagnosis (mean)	2.04	2.09	2.09	2.19	0.75	1.52	1.85	1.93
Absence of MCAs	77 (28.3)	59 (28)	23 (27.1)	15 (19.2)	0,27	21 (43.8)	16 (34.8)	2 ((13.3)
Molecular – Sequencing of <i>KIT</i> gene								
<i>KIT</i> point mutation at codon 816	28 (42.4)	28 (48.3)	11 (47.8)	12 (46.2)	1	5 (55.6)	0 (0)	0 (0)
Other <i>KIT</i> mutations	28 (42.4)	22 (37.9)	9 (39.2)	10 (38.5)	1	3 (33.3)	3 (75)	3 (75)
<i>KIT</i> WT	10 (15.2)	8 (13.8)	3 (13)	4 (15.4)	1	1 (11.1)	1 (25)	1 (25)
Biological								
Level of baseline tryptase [mean ($\mu\text{g}\cdot\text{L}^{-1}$), range, number of patients]	7.52 [1 – 60] (n=121)	7.36 [1- 45.2] (n=101)	7.23 [1.5- 23.1] (n=48)	7.55 [1- 45.2] (n=42)	0.82	7.60 [2.9- 18.3] (n=11)	4.32 [1.3 – 11.5] (n=16)	23.99 [2- 60] (n=4)

Table 2. Main mast cell activation symptoms at baseline, as a function of the type of cutaneous mastocytosis

	MPCM (n/total %) n = 211	Mastocytoma (n/total %) n = 46	DCM (n/total %) n = 15	p.value (MPCM vs Mastocytoma)	p.value (MPCM vs DCM)
Cutaneous signs:					
Pruritus/Flushes	86 (40.8)	21 (45.7)	11 (73.3)	0.62	0.016*
Urticaria	5 (2.4)	1 (2.2)	1 (6.7)	1	0.34
Digestive symptoms: anorexia, abdominal pain, diarrhea , nausea and /or vomiting	72 (34.1)	11 (23.9)	4 (26.7)	0.22	0.78
Food reactions	32 (15.2)	7 (15.2)	1 (6.7)	1	0.70
Loss of consciousness, drained feeling and/or episodes of pallor	44 (20.9)	7 (15.2)	2 (13.3)	0.54	0.74
Sleep disorders and/or nightmares	17 (8.1)	3 (6.5)	1 (6.7)	1	1
Muscle/joint/bone pain(s)	18 (8.5)	3 (6.5)	2 (13.3)	1	0.63
Emotional disturbance or behavioral disorders	2 (0.9)	1 (2.2)	0 (0)	0.45	1
Pollakiuria	5 (2.4)	1 (2.2)	0 (0)	1	1

Table 3. Congenital vs. non-congenital mastocytosis

Characteristics	Congenital group n = 127 (n/total %)	Non-congenital group n = 145 (n/total %)	p.value
Clinical			
Females	52 (40.9)	70 (48.3)	0.271
Males	75 (59.1)	75 (51.7)	
Sex ratio (M/F)	1.4	1.07	
Mean age at diagnosis (days)	1237.3	1371.3	0.544 (t test)
Familial mastocytosis	8 (6.3)	15 (10.3)	0.28
MPCM	90 (70.9)	121 (83.4)	0.019 *
-Large (polymorphic lesions)	44 (48.9)	41 (33.9)	0.033*
-Small (<0.5cm)	27 (30)	51 (42.1)	0.084
-NC	19 (21.1)	29 (24)	0.34
Mastocytoma	27 (21.3)	19 (12.9)	0.26
DCM	10 (7.9)	5 (3.4)	0.12
Molecular – Sequencing of <i>KIT</i> gene	29 (22.8)	37 (25.5)	
<i>KIT</i> point mutation at codon 816	12 (41.4)	16 (43.2)	0.93
Other <i>KIT</i> mutations	13 (44.8)	15 (40.5)	0.804
<i>KIT</i> WT	4 (13.8)	6 (16.2)	1
Biological			
Level of baseline tryptase [mean ($\mu\text{g}\cdot\text{L}^{-1}$), range, number of patients]	8.92 [1-60] (n=52)	6.53 [1.1-28.2] (n=69)	0.1

Table 4. Univariate analysis – clinical, biological and molecular variables associated with the progression of cutaneous mastocytosis

Variables	Odds Ratio	95% CI	p.value
Clinical			
Sexe	1.46	[0.786-2.72]	0.230
Age at onset	1.18	[0.374-3.14]	0.833
Congenital mastocytosis	0.476	[0.236-0.917]	0.031*
Familial mastocytosis	1.18	[0.374-3.14]	0.757
Mastocytoma	0.594	[0.215-1.40]	0.268
MPCM	1.03	[0.502-2.25]	0.941
Number of MCAs at diagnosis	1.12	[0.997-12.6]	0.051
Presence of MCAs at diagnosis	2.20	[1.05-5.06]	0.047*
¹ Pruritus	0.19	[0.072-0.43]	0.000***
Flush	0.3	[0.128-0.663]	0.004**
Aggravation/Stability of MCAs	3.36	[1.28-9.13]	0.015*
Regression/healing of MCAs	1.92	[8.88 × 10 ⁻¹ -4.53]	0.112
Biological			
Tryptase	1.01	[0.958-1.07]	0.566
Molecular – Sequencing of <i>KIT</i> gene			
<i>KIT</i> point mutation at codon 816	0.173	[0.025-0.719]	0.031*
Other <i>KIT</i> mutation	2.07	[0.627-7.15]	0.235
<i>KIT</i> WT	3.00	[0.666-12.6]	0.135

Table 5. Univariate analysis – clinical, biological and molecular variables associated with the progression of MCAs

Variables	Odds Ratio	95% CI	p.value
Clinical			
Sexe	1.03	[0.601-1.76]	0.923
Age at onset	1.00	[1.00-1.00]	0.142
Congenital mastocytosis	0.815	[0.476-1.400]	0.454
Familial mastocytosis	3.03	[0.998-1.31]	0.081
Mastocytoma	0.718	[0.368-1.44]	0.339
MPCM	1.09	[0.569-2.03]	0.788
Number of MCAs at diagnosis	653	[1.18.10²-1.24.10⁴]	0.000***
¹ Urticaria	4.97	[1.05-26.2]	0.041*
Aggravation/Stability of CM	2.20	[1.05-5.06]	0.047*
Biological			
Tryptase	1.05	[0.973-1.17]	0.341
Molecular – Sequencing of <i>KIT</i> gene			
<i>KIT</i> point mutation at codon 816	1.53	[0.427-6.33]	0.525
Other <i>KIT</i> mutation	0.469	[0.124-1.66]	0.243
<i>KIT</i> WT	2.25	[0.363-4.37]	0.464

¹Other types of MCAs (digestive symptoms, pain, drained feeling etc.) were not significantly associated with the overall progression of MCAs (data not shown)

Table 6. A comparison of clinical, biological and molecular markers in patient group 1 (correlated regression of both CM and MCAs) and patient group 2 (no correlation)

N = 142 patients with CM regression and changes in MCAs	Groupe 1 n= 115 (n/total %)	Groupe 2 n = 27 (n/total %)	p.value
Clinical			
Sex ratio (M/F)	1.25	1.45	0.83
Familial mastocytosis	14 (12.2)	1 (3.7)	0.0097
Congenital mastocytosis	48 (41.7)	12 (44)	0.34
MPCM	89 (77.4)	23 (85.2)	0.44
Large	38	6	0.16
Small	37	10	1
NC	14	7	0.13
Mastocytoma	20 (17.4)	3 (13)	0.57
DCM	6 (5.2)	1 (3.7)	1
Number of MCAs at diagnosis	2.5 [1– 11]	1,97 [0 - 4]	0.0002***
Cutaneous signs: Pruritus/Flushes/Urticaria	81 (70.4)	12 (44.4)	0.014*
Digestive symptoms: anorexia, abdominal pain, diarrhea, nausea and /or vomiting	58 (50.4)	10 (37.0)	0.28
Discomfort, loss of consciousness, drained feeling and/or episodes of pallor	35 (30.4)	4 (14.8)	0.15
Food reaction	28 (24.3)	4 (14.8)	0.44
Bone, joint and/or muscular pain(s)	15 (13)	0 (0)	0.074
Biological			
Level of baseline tryptase [mean ($\mu\text{g.L}^{-1}$), range, number of patients]	7.54 [1 - 45.2] (n=64)	7.75 [1.5-28.2] (n=11)	0.379
Molecular – Sequencing of <i>KIT</i> gene	n=36	n=6	-
Other <i>KIT</i> mutations	13 (36.1)	3 (50)	-
<i>KIT</i> point mutation at codon 816	18 (50)	3 (50)	-
<i>KIT</i> WT	5 (13.4)	0 (0)	-