

Gastrointestinal manifestations in mastocytosis: A study of 83 patients

Harry Sokol, MD, PhD,^{a,b,c,d,*} Sophie Georgin-Lavialle, MD, PhD,^{d,e,f,*} Danielle Canioni, MD,^{f,g,*} Stéphane Barete, MD, PhD,^h Gandhi Damaj, MD,^{d,i} Erinn Soucie, PhD,^j Julie Bruneau, MD,^{f,g} Marie-Olivia Chandesris, MD,^d Felipe Suarez, MD, PhD,^k Jean-Marie Launay, PharmD, PhD,^l Achille Aouba, MD,^k Catherine Grandpeix-Guyodo, MD,^d Fanny Lanternier, MD,^m Bernard Grosbois, MD,ⁿ Christian de Gennes, MD,^o Pascal Cathébras, MD,^p Olivier Fain, MD,^q Nadia Hoyeau-Idrissi, MD,^r Patrice Dubreuil, PhD,^{d,i} Olivier Lortholary, MD, PhD,^{d,m} Laurent Beaugerie, MD, PhD,^a Brigitte Ranque, MD, PhD,^s and Olivier Hermine, MD, PhD^{c,d,i} Paris, Jouy en Josas, Amiens, Marseille, Rennes, Saint-Etienne, and Bondy, France

Background: Mastocytosis is a heterogeneous disease characterized by mast cell accumulation in 1 or more organs. Gastrointestinal manifestations of systemic mastocytosis have been previously studied in small cohorts of patients, and no specific histologic description is available.

Objective: We sought to assess the clinical and pathologic features of gastrointestinal manifestations in patients with mastocytosis.

Methods: Medical history and gastrointestinal symptoms of patients with mastocytosis (n = 83) were compared with those of matched healthy subjects (n = 83) by means of patient questionnaire. Data were analyzed for epidemiologic, clinical, biological, and genetic factors associated with gastrointestinal symptoms for patients with mastocytosis. A comparative analysis of gastrointestinal histology from patients with mastocytosis (n = 23), control subjects with inflammatory bowel disease (n = 17), and healthy subjects (n = 19) was performed. **Results:** The following gastrointestinal symptoms occurred more frequently and were more severe in patients with mastocytosis than in healthy subjects: bloating (33% vs 7.2%, $P < .0001$), abdominal pain (27.3% vs 4.8%, $P < .0001$), nausea

(23% vs 8.4%, $P = .02$), and diarrhea (33.85% vs 1.2%, $P < .0001$). Patients with mastocytosis had a significantly higher incidence of personal history of duodenal ulcer ($P = .02$). Wild-type (WT) *c-Kit* was associated with diarrhea ($P = .03$). Specific histologic lesions were present in patients with mastocytosis but were not correlated with clinical symptoms. **Conclusion:** Gastrointestinal manifestations in patients with mastocytosis are highly prevalent and often severe. Clinical symptoms do not correspond to histologic findings, are nonspecific, and can simulate irritable bowel syndrome. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: Mastocytosis, mast cells, *c-Kit*, gastrointestinal tract

Mastocytosis is a heterogeneous group of disorders characterized by abnormal growth and accumulation of mast cells (MCs) in 1 or more organ systems.^{1,2} Diagnostic criteria and classification were updated by the World Health Organization in 2008.³ This classification defines 7 disease variants: cutaneous mastocytosis, indolent systemic mastocytosis (SM), SM with an associated

From ^aService de Gastroentérologie et Nutrition, Hôpital Saint-Antoine, AP-HP, Université Pierre et Marie Curie-Paris 6, Paris; ^bEquipe AVENIR, Laboratoire INSERM U1057/UMR CNRS 7203, Université Pierre et Marie Curie 6, Paris; ^cEquipe Interactions des bactéries commensales et probiotiques avec l'hôte, MICALIS, INRA, Jouy en Josas; ^dCentre de Référence des Mastocytoses, Faculté de Médecine et AP-HP Necker-Enfants Malades, Paris; ^eService de Médecine Interne, Hôpital Tenon, Université Pierre et Marie Curie-Paris 6, Paris; ^fCNRS UMR 8147, Hôpital Necker-Enfants malades, Paris; ^gLaboratoire d'Anatomie-Pathologie, Université Paris Descartes, Paris Sorbonne Cité, Faculté de Médecine et AP-HP Necker-Enfants Malades, Paris; ^hService de Dermatologie, Hôpital Tenon, Université Pierre et Marie Curie-Paris 6 et AP-HP, Paris; ⁱService d'Hématologie, Centre Hospitalier Universitaire Université de Picardie, Hôpital sud, Amiens; ^jINSERM, U1068, CRCM (Signaling, Hematopoiesis and Mechanism of Oncogenesis), Institut Paoli-Calmettes, Aix-Marseille University, F-13284, CNRS, UMR7258, Marseille; ^kService d'Hématologie Adultes, Université Paris Descartes, Paris Sorbonne Cité, Faculté de Médecine et AP-HP Necker-Enfants Malades, Paris; ^lLaboratoire de Biochimie et Biologie Moléculaire, Hôpital Lariboisière, Université Paris VII et AP-HP, Paris; ^mService des Maladies infectieuses et tropicales, Université Paris Descartes, Paris Sorbonne Cité, Faculté de Médecine et AP-HP Necker-Enfants Malades, Centre d'Infectiologie Necker Pasteur, Paris; ⁿService de médecine interne, CHU Hôpital Sud, Rennes; ^oService de médecine interne, AP-HP, Université Paris 6, CHU Pitié Salpêtrière, Paris; ^pService de médecine interne, Hôpital Nord, Saint-Etienne; ^qService de médecine interne, Hôpital Jean Verdier, Université Paris 13 et AP-HP, Bondy; ^rService d'Anatomopathologie, AP-HP Saint-Antoine, Université Pierre et Marie Curie-Paris 6, Paris; and ^sService de médecine Interne, Hôpital Européen Georges Pompidou, Université Paris Descartes, Paris Sorbonne Cité, AP-HP, Paris.

*These authors contributed equally to this work.

Supported by Association Française pour les Initiatives et la Recherche sur le Mastocyte et les Mastocytoses (AFIRMM), Cancéropole de l'île de France. S.G.-L. is a recipient

of a fellowship from CNRS-AP-HP. This work was financed by INSERM, la Ligue Nationale Contre le Cancer équipe labellisée (to P.D.), MRT (to P.D. and O.H.), and INCA (to P.D. and O.H.).

Disclosure of potential conflict of interest: H. Sokol has consultancy arrangements with Enterome and with Danone. G. Damaj is a Board member for Mundipharma and has received one or more grants from or has one or more grants pending with Mundipharma and Roche. J.-M. Launay has received one or more grants from or has one or more grants pending with PHRC C07-33 Gènes et autisme. F. Lanternier has received one or more payments for lecturing from or is on the speakers' bureau for and has received one or more payments for travel/accommodations/meeting expenses from Gilead Science and MSD. B. Grosbois is a Board member for Octapharma. P. Dubreuil has been supported by one or more grants from INCA and Ligue nationale Contre le Cancer and is employed by and owns stock/stock options in AB Science. L. Beaugerie has consultancy arrangements with Abbott and has received one or more payments for the development of educational presentations for Abbott, MSD, and Ferring Pharmaceuticals. O. Hermine has been supported by one or more grants from Ligue contre le cancer et INCA. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication January 30, 2013; revised May 20, 2013; accepted for publication May 24, 2013.

Corresponding author: Olivier Hermine, MD, PhD, Service d'Hématologie Adultes, CNRS UMR 8147 et Centre de Référence sur les Mastocytoses, Hôpital Necker-Enfants malades, Université Paris Descartes, Assistance Publique-Hôpitaux de Paris, 149 Rue des Sèvres, 75743 Paris Cedex 15, France. E-mail: ohermine@gmail.com.

0091-6749/\$36.00

© 2013 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaci.2013.05.026>

Abbreviations used

MC: Mast cell
SM: Systemic mastocytosis
WT: Wild-type

clonal hematologic non-MC lineage disease, aggressive SM, MC leukemia, MC sarcoma, and extracutaneous mastocytoma. SM is defined by major and minor criteria. If at least 1 major and 1 minor or at least 3 minor criteria are fulfilled, the diagnosis of SM is established. Criteria defining the MC burden, involvement of non-MC lineages, and aggressiveness of the disease (C-Findings including: marked cytopenia; osteolysis with or without pathologic fracture; ascites and elevated liver enzymes, malabsorption plus hypoalbuminemia) are applied to subclassify SM.^{1,2,4}

MC neoplasms are related to the clonal proliferation of MCs secondary to a gain-of-function mutation of the proto-oncogene *c-Kit*.⁵ Adults with mastocytosis usually present D816V mutations in *c-Kit*, the tyrosine kinase receptor of stem cell factor (SCF) expressed on MCs,^{6,7} but the mechanisms that drive the multiple phenotypic and clinical manifestations of this myeloproliferative disorder are not clear. Currently, expression of CD2, CD25, or both by MCs is considered pathognomonic evidence for the pathologic status of MCs, and thus it is used as a minor criterion for the diagnosis of MC disorders.

Clinical manifestations of mastocytosis are variable⁸ and related to the release of MC mediators or pathologic MC infiltration. Although indolent systemic and pure cutaneous forms are not associated with reduced life expectancy,⁹ both clinical forms are associated with significant disabilities.¹⁰ Previous studies reported gastrointestinal symptoms in 20% to 80% of patients with mastocytosis,¹¹⁻¹⁶ but available data are based on old studies with small sample sizes.

The objectives of this study were to describe subjective and objective gastrointestinal manifestations in a large cohort of patients with mastocytosis (n = 83) and to study gastrointestinal biopsy specimens of patients with SM and compare these data with those of healthy age-matched control subjects.

METHODS**Patients**

Eighty-three consecutive patients (24 men and 59 women) with mastocytosis, as defined by the World Health Organization criteria,³ and age-matched healthy control subjects were enrolled in a national multicenter study between 2006 and 2010 (see Table E1 in this article's Online Repository at www.jacionline.org). All patients were included in the mastocytosis pathophysiologic study, which started in 2003 and is sponsored by AFIRMM (Association Française pour les Initiatives et la Recherche sur le mastocyte et la Mastocytose). Mastocytosis subcategories comprised cutaneous SM, indolent SM, aggressive SM, and systemic mastocytosis with an associated clonal hematologic non-MC lineage disease (Table I). Characteristics of patients with mastocytosis are described in Table I. The study was approved by the Necker Hospital Ethics Committee and carried out according to the Helsinki convention. All patients provided informed consent.

Data collection

For the cohort of patients with mastocytosis, all adults (≥18 years) identified by the AFIRMM between 1999 and 2010 as having mastocytosis were eligible. All questionnaires were returned to and processed at the Hematology Department in Necker Hospital (Paris, France). Data from

questionnaires were collected according to French privacy laws, and the Ethics Committee of Necker Hospital approved all parts of the study.

Study design and objectives

We were looking for a clear picture of the type and severity of these symptoms. A questionnaire regarding gastrointestinal history and symptoms was then developed by a group of experts involved in the care of patients with mastocytosis in collaboration with a gastroenterologist (see Fig E1 in this article's Online Repository at www.jacionline.org) and was completed by patients with mastocytosis.

The study consisted of several aspects:

1. *Case-control study evaluating gastrointestinal history and symptoms in patients with mastocytosis.* Healthy control subjects were matched to patients with mastocytosis according to sex and age (± 5 years). The control cohort included members from the medical staff or their families who were unaffected by mastocytosis and had no familial history of the disease. Patients with mastocytosis and control subjects were asked to respond to the same questionnaire regarding gastrointestinal history and symptoms.
2. *Identification of factors associated with gastrointestinal symptoms.* Analysis was performed on those patients with mastocytosis who responded to the questionnaire to identify clinical, biological (ie, serum tryptase level), and genetic (ie, *c-Kit* mutation) factors associated with gastrointestinal symptoms.
3. *Study of gastrointestinal pathologic features in patients with mastocytosis.* Biopsy specimens of the gastrointestinal tract were collected by means of endoscopy from a subgroup of patients with mastocytosis. These samples were compared with biopsy specimens taken from healthy subjects (patients undergoing endoscopies but without abnormalities) and patients with inflammatory bowel disease (IBD) with typical histologic lesions.

Measurable parameters of disability

Five measurable parameters were selected to confirm disability in patients with mastocytosis. These included 2 quantifiable disabilities: number of flushing episodes per week and number of micturitions per day. In addition, 3 scores used to measure disability in patients with other pathologies were assessed: a pruritus score,¹⁰ the Hamilton score for depression,¹⁷ and the QLQ-C30 quality-of-life score.¹⁸ For these measures, the following were considered as indicating a disability: 7 or more flushes per week, 8 or more micturitions per day (pollakiuria), a pruritus score of 6 or greater, a Hamilton score of 10 or greater (depression), and a QLQ-C30 score of 60 or greater.

Histologic and immunohistochemical techniques

Twenty-three patients of this series had gastrointestinal tract biopsies, and the obtained specimen were compared with those of 36 control subjects (19 normal specimens and 17 inflammatory specimens from patients with chronic IBD) to evaluate the specificity of the lesions observed in our patients with SM. Gastrointestinal tract biopsy specimens were analyzed by one pathologist (D.C.), with a particular focus on MCs. They were performed in different sites of the gastrointestinal tract from the esophagus to the rectum. Each sample was fixed in 10% formalin, and slides were analyzed after hematoxylin and eosin and Giemsa staining. Immunohistochemistry was performed by using the ABC method with an automated stainer (Leica Bond, Menarini) with antibodies targeting MCs: anti-CD117 and anti-tryptase antibodies (1:400; Dakopatts, Glostrup, Denmark) and anti-CD25 antibody (1L50; Novocastra, Newcastle upon Tyne, United Kingdom).

For each specimen, MC numbers were counted on CD117 staining of 5 different high-power fields ($\times 400$ magnification) of each digestive site. The repartition of MCs in the lamina propria was also studied. The number of eosinophils in the lamina propria was also counted on 5 high-power fields in different digestive biopsy specimens. Finally, the MC/inflammatory cell ratio in the lamina propria was determined in all gastrointestinal biopsy specimens.

TABLE I. Main features of the 83 patients with mastocytosis

Demography		
Age on diagnosis (y), median (minimum-maximum range)	34.7 (0-66)	
Age on the beginning of symptoms (y), median (minimum-maximum range)	29 (0-66)	
Age on study (y), mean (minimum-maximum range)	52 (22-81)	
Delay between beginning of symptoms and study, median (minimum-maximum range)	7.5 (0-35)	
Sex, no. (%)	Men: 24 (28.9) Women: 59 (71)	
Treatment		
H ₁ -antihistamine, no. (%)	36 (43.4)	
H ₂ -antihistamine, no. (%)	9 (10.8)	
Proton pump inhibitors, no. (%)	4 (4.8)	
IFN- α , no. (%)	1 (1)	
Cladribine, no. (%)	6 (7.2)	
Mastocytosis characteristics and non-gastrointestinal symptoms		
Anaphylactic shock, no. (%)	3 (3.6)	
Flush/day, median (minimum-maximum range)	2.5 (0-10)	
Pollakiuria, no. (%)	38 (45.8)	
Pollakiuria/day, median (minimum-maximum range)	7.3 (2-24)	
Itching score, median (minimum-maximum range)	8.5 (0-21)	
Hamilton score, median (minimum-maximum range)	12.4 (0-34)	
QOL score, median (minimum-maximum range)	62.3 (34-102)	
OPA score, median (minimum-maximum range)	2 (0-3)	
World Health Organization classification	CM*: n = 14 (17%) ISM: n = 61 (73.6%) SM-AHNMD: n = 1 (1%) ASM: n = 7 (8.4%)	
<i>c-Kit</i> mutation	D816V: n = 63 (75.9%) WT: n = 15 (18%) Not done: n = 5 (6%)	
Serum tryptase rate (ng/mL), median (minimum-maximum range)	24.2 (1-1828)	

ASM, Aggressive systemic mastocytosis; CM, cutaneous mastocytosis; ISM, indolent systemic mastocytosis; SM-AHNMD, systemic mastocytosis with an associated clonal hematologic non-MC lineage disease.

*Some or all of the patients classified as having cutaneous mastocytosis might actually have indolent systemic mastocytosis if they had bone marrow biopsies performed.

Bone marrow preparation, D816V *c-Kit* mutation detection, and serum tryptase measurement

After aspiration, fresh bone marrow underwent red blood cell lysis by using ammonium chloride. Then RNA extraction was performed with the Rneasy Mini Kit (reference 74104; Qiagen, Hilden, Germany). cDNA was neo-synthesized by using the AffinityScript Multiple Temperature cDNA Synthesis Kit (reference 200436; Agilent, Santa Clara, Calif). The D816V *c-Kit* mutation was determined as previously described.^{19,20} Total serum tryptase (protryptase plus β -tryptase) levels were measured with a fluorescent enzyme-linked immunoassay (UniCAP; Pharmacia, Uppsala, Sweden).²¹ The detection limit of this assay is 1 ng/mL, and in healthy control subjects serum tryptase levels range between less than 1 and 15 ng/mL, with a median of approximately 5 ng/mL.²²

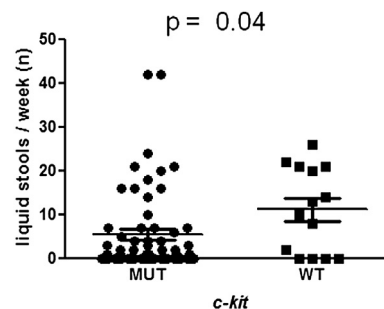
Statistical analysis

The case-control study compared the prevalence of gastrointestinal history or symptoms in 83 patients with mastocytosis and 83 matched control subjects by using conditional logistic regression. In 83 patients with mastocytosis, we

TABLE II. Gastrointestinal symptoms and history of patients with mastocytosis and matched controls

	Patients with mastocytosis (n = 83)	Control subjects (n = 83)	P value
Age on study (y), mean (SD)	52.0 (12.9)	52.0 (12.7)	.99
Male sex, no. (%)	24 (28.9)	24 (28.9)	1
Medical history, no. (%)			
Crohn disease	0	0	1
Ulcerative colitis	1 (1.2)	2 (2.4)	1
Celiac disease	1 (1.2)	0	.5
Gastric ulcer	6 (7.4)	2 (2.4)	.13
Duodenal ulcer	5 (6.2)	0	.02
Gastric or duodenal ulcer	9 (11.4)	2 (2.4)	.02
Colorectal cancer	1 (1.2)	0	.5
Gastrointestinal symptoms			
Any gastrointestinal symptom,* no. (%)	49 (59.0)	16 (19.3)	<.0001
Bloating score, mean (SD)	4.2 (3.3)	1.7 (2.4)	<.0001
Bloating score >5, no. (%)	26 (33.3)	6 (7.2)	<.0001
Abdominal pain score, mean (SD)	3.6 (3.1)	1.0 (1.8)	<.0001
Abdominal pain score >5, no. (%)	21 (27.3)	4 (4.8)	<.0001
Nausea score, mean (SD)	3.3 (3.05)	0.1 (0.5)	<.0001
Nausea score ≥ 1 , no. (%)	18 (23.4)	7 (8.4)	.009
Vomiting score, mean (SD)	0.3 (1.2)	0.04 (0.24)	.11
Vomiting score ≥ 1 , no. (%)	6 (7.8)	2 (2.4)	.16
Diarrhea score, mean (SD)	6.2 (9.4)	0.3 (1.6)	<.0001
Diarrhea score ≥ 5 , no. (%)	27 (33.8)	1 (1.2)	<.0001
Blood in stool, no. (%)	14 (18.7)	18 (21.7)	.6
Gastrointestinal endoscopy, no. (%)			
Upper gastrointestinal endoscopy	42 (55.3)	13 (15.7)	<.0001
Colonoscopy	43 (51.8)	14 (17.1)	<.0001

*A bloating score of greater than 5, an abdominal pain score of greater than 5, a nausea score of 1 or greater, a vomiting score of 1 or greater, or a diarrhea score of 5 or greater.

**FIG 1.** Number of liquid stools per week reported for patients with mastocytosis grouped according to WT or mutated (*MUT*) *c-Kit* detected in skin lesions.

looked for associations among the 3 main gastrointestinal symptoms encountered in mastocytosis (nausea, diarrhea, and abdominal pain encoded as binary variables) and quality-of-life scores, *c-Kit* mutation, and serum tryptase levels. Associations with binary variables were tested by using the χ^2 test (or the Fisher test when appropriate), and associations with quantitative variables were tested by using the Wilcoxon test. Correlations were evaluated by using the nonparametric Spearman correlation test. All statistical analyses were performed with R software (<http://cran.r-project.org/>, version 2.11.3).

RESULTS

Eighty-three patients and age-matched healthy control subjects answered our questionnaire. Among the 23 patients

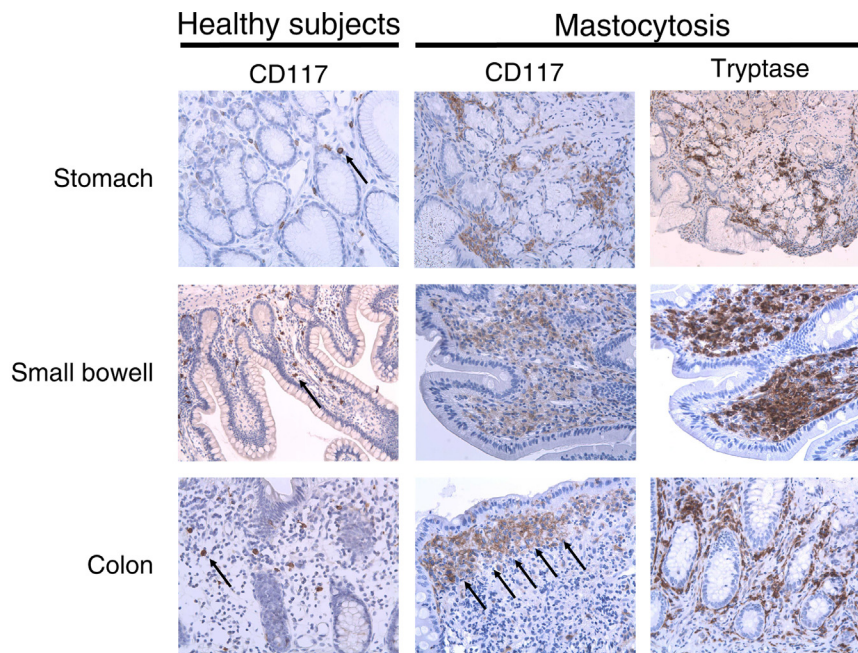


FIG 2. Examples of MC infiltration of the gastrointestinal tract. Biopsy specimens of the stomach, small bowel, and colon from healthy subjects and patients with mastocytosis undergoing immunohistochemistry with anti-CD117 antibody (Gx200) and anti-tryptase antibody (Gx100 for stomach biopsy specimens and Gx200 for small bowel and colon biopsy specimens) are shown. *Black arrows* show MCs.

with mastocytosis who had undergone endoscopic examination, 197 biopsy specimens from different sites in the gastrointestinal tract were available for analysis. These biopsy specimens were compared with 61 normal biopsy specimens from 19 healthy subjects and 54 biopsy specimens with histologic inflammation from 17 patients with IBD having typical histologic lesions.

Gastrointestinal history and symptoms in mastocytosis: Case-control study

The gastrointestinal history and symptoms of 83 patients with mastocytosis were compared with those of 83 sex- and age-matched healthy subjects (Table II).

Patients with mastocytosis presented with significantly more frequent personal history of ulcers ($P = .025$), especially duodenal ulcers ($P = .02$). Regarding gastrointestinal symptoms, bloating, abdominal pain, nausea, vomiting, and liquid stools were more frequent in patients with mastocytosis than in matched healthy subjects. Upper and lower gastrointestinal tract endoscopies had been performed more frequently in patients with mastocytosis than in matched control subjects.

Factors associated with gastrointestinal symptoms in patients with mastocytosis and effect on quality of life

We looked for an association between gastrointestinal symptoms and tryptase levels or *c-Kit* mutation in patients with mastocytosis. The only significant association we observed was a higher number of liquid stools in patients with WT *c-Kit* (Fig 1).

We then investigated whether gastrointestinal symptoms were associated with an altered quality of life. We observed that both bloating and abdominal pain scores correlated significantly with

quality-of-life scores ($P = .001$ and $P = .0004$, respectively, Spearman correlation).

Gastrointestinal pathologic features in patients with mastocytosis with gastrointestinal symptoms

The gastrointestinal pathologic features of patients with mastocytosis, control subjects with IBD, and healthy subjects are summarized in Table III.

MC aggregates (ie, ≥ 15 MCs) were observed only in patients with mastocytosis (Fig 2). MCs were usually scattered in healthy subjects and control subjects with IBD, in whom MCs were also frequently increased, whereas MCs were more specifically localized (MC aggregates, localization of MCs in a specific area of the biopsy specimen, or both) in 23.5% to 74.3% of patients with mastocytosis, depending on the biopsy site. In patients with mastocytosis, MCs were notably located in the villi or in pericryptic or subcryptic areas. The absolute number of MCs was variable in patients with mastocytosis, but in all gastrointestinal topography, the mean absolute number was always higher in these patients compared with numbers seen in healthy control subjects (Table III). This number was counted on c-Kit staining and was similar to the number of MCs on tryptase staining.

MCs often represented the major cell type in the cellular infiltrate in patients with mastocytosis. By contrast, in control subjects with IBD, even if MC numbers were frequently increased, the MC/inflammatory cell ratio was always less than 50%. Histologic inflammation was frequently lacking or mild in patients with mastocytosis. Eosinophilic infiltrate was similar in all 3 cohorts.

MC aggregates were more specifically localized in the top of the villi or in a band under the crypts or in the periglandular region in patients with mastocytosis. An MC/inflammatory cell ratio in favor of MCs was also a frequent histologic feature associated

TABLE III. Gastrointestinal pathologic features of patients with mastocytosis, control subjects with IBD, and healthy subjects: stomach, duodenum, ileum, and rectum and colon

	Healthy control subjects	Control subjects with IBD	Patients with mastocytosis	P value, HC vs M	P value, IC vs M
Stomach					
No. of subjects	7	5	18		
Histologic inflammation, % (no.) [‡]					
None or mild	100% (7)	0	83% (15)	1	.0008
Moderate to severe	0	100% (5)	5.5% (1)		
MCs, no.* ± SEM	17.9 ± 1.8	27.8 ± 5.1	20.5 ± 5.1	.80	.08
MC aggregate [†] (% of subjects)	0	0	23.5% (4)	.28	.53
MCs in submucosa (% of subjects)	0	80% (4)	41.2% (7)	.065	.31
MC topography, % (no.)					
Scattered	100% (7)	100% (5)	76.5% (13)	.28	.53
Localized	0	0	23.5% (4)		
MC-specific topography, % (no.)					
Periglandular	0	0	22.2% (4)	NA	
CD25 ⁺ MCs (% of subjects)	0	0	27.7% (5)	NA	
Proportion of MCs in cellular infiltrate (% of subjects) [§]					
Majority	28.6% (2)	0	70.6% (12)	.085	.009
Minority	71.4% (5)	100% (5)	29.4% (5)		
Eosinophils, mean ± SEM	3.2 ± 0.7	2.5	4.12 ± 1.3	.91	.43
Duodenum					
No. of subjects	7	5	16		
Histologic inflammation, % (no.) [‡]					
None or mild	100% (7)	0	62.5% (10)	.12	.035
Moderate to severe	0	100% (5)	37.5% (6)		
Villous atrophy					
Partial	0	60% (3)	25% (4)		
Subtotal - total	0	20% (1)	0		
All	0	80% (4)	25% (4)	.27	.047
MCs, no.* ± SEM	24.1 ± 2.7	29.0 ± 6.3	40.3 ± 6.1	.08	.28
MC aggregate [†] (% of subjects)	0	0	31.3% (5)	.27	.28
MCs in submucosa (% of subjects)	0	80% (4)	56.3% (9)	.019	.61
MC topography, % (no.)					
Scattered	100% (7)	100% (5)	31.3% (5)	.005	.012
Localized	0	0	68.7% (11)		
MC-specific topography, % (no.)					
Periglandular	0	0	62.5% (10)	NA	
Villi	0	0	56.3% (9)		
CD25 ⁺ MCs (% of subjects)	0	0	50% (8)	NA	
Proportion of MCs in cellular infiltrate (% of subjects) [§]					
Majority	14.3% (1)	0	31.3% (5)	.62	.28
Minority	85.7% (6)	100% (5)	68.7% (11)		
Eosinophils, mean ± SEM	8.6 ± 3.9	10.5 ± 4.1	7.2 ± 1.7	.88	.33
Ileum					
No. of subjects	7	5	9		
Histologic inflammation, % (no.) [‡]					
None or mild	100% (7)	0	88.9% (8)	1	.003
Moderate to severe	0	100% (5)	11.1% (1)		
Villous atrophy					
Partial	0	20% (1)	0		
Subtotal - total	0	0	0		
All	0	20% (1)	0	1	.36
MCs, no.* ± SEM	28.4 ± 2.7	39.0 ± 4.3	45.7 ± 3.5	.012	.20
MC aggregate [†] (% of subjects)	0	0	22.2% (2)	.48	.51
MCs in submucosa (% of subjects)	0	100% (5)	55.6% (5)	.034	.22
MC topography, % (no.)					
Scattered	100% (7)	100% (5)	33.3% (3)	.01	.031
Localized	0	0	66.7% (6)		
MC-specific topography, % (no.)					
Periglandular	0	0	55.5% (5)	NA	
Villi	0	0	55.6% (5)		
CD25 ⁺ MCs (% of subjects)	0	0	44% (4)	NA	

(Continued)

TABLE III. (Continued)

	Healthy control subjects	Control subjects with IBD	Patients with mastocytosis	P value, HC vs M	P value, IC vs M
Proportion of MCs in cellular infiltrate (% of subjects) [§]					
Majority	28.6% (2)	0	77.8% (7)	.13	.01
Minority	71.4% (5)	100% (5)	22.2% (2)		
Eosinophils, mean $\pm$ SEM	7.5 $\pm$ 2.2	11.0 $\pm$ 8.5	7.9 $\pm$ 2.3	.91	.28
Rectum and colon					
No. of subjects	5	8	14		
Histologic inflammation, % (no.) [‡]					
None or mild	100% (5)	0	64.3% (9)	.26	.006
Moderate to severe	0	100% (8)	35.7% (5)		
MCs, no.* $\pm$ SEM	14.4 $\pm$ 3.1	28.3 $\pm$ 3.8	45.1 $\pm$ 8.8	.023	.31
MC aggregate [†] (% of subjects)	0	0	42.9% (6)	.13	.05
MCs in submucosa (% of subjects)	0	100% (8)	50% (7)	.11	.022
MC topography, % (no.)					
Scattered	100% (5)	100% (8)	25.7% (5)	.032	.006
Localized	0	0	74.3% (9)		
MC-specific topography, % (no.)					
Periglandular	0	0	64.2% (9)	NA	
CD25 ⁺ MCs (% of subjects)	0	0	64.2% (9)	NA	
Proportion of MCs in cellular infiltrate (% of subjects) [§]					
Majority	0	0	57.1% (8)	.045	.018
Minority	100% (5)	100% (8)	42.9% (6)		
Eosinophils, mean $\pm$ SEM	10.5 $\pm$ 5.8	10.3 $\pm$ 5.5	7.3 $\pm$ 1.9	.81	.71

Statistical significance is indicated by boldface.

NA, Not available.

*Number of MCs counted on 5 fields/high-power field (Gx400).

[†]Aggregate means at least 5 MCs.

[‡]Histologic inflammation: presence of an inflammatory infiltrate usually made of plasma cells and lymphocytes associated with more or less eosinophils.

[§]Majority = MCs are more numerous than other inflammatory cells; minority = MCs are less numerous than other inflammatory cells.

with mastocytosis. These symptoms in patients with scattered and localized MCs were compared to investigate whether MC infiltration was involved in gastrointestinal symptoms (see Table E2 in this article's Online Repository at www.jacionline.org). No clear correlation between MC infiltration and gastrointestinal symptoms was observed, except for an association between diarrhea and scattered MC infiltrates in the stomach. Interestingly, gastroduodenal ulcer history was associated with localized MC infiltrates in the stomach.

CD25 expression on MCs

For CD25, we only took into account CD25 staining for digestive biopsy specimens in which control cells were also stained. Slides that were totally negative for CD25 were excluded. CD25 was highly expressed among MCs of patients with SM ($n = 13/19$) with abundant digestive infiltration. When patients presented with low digestive MC infiltration, CD25 expression on MCs was negative or very rare ($n = 5/19$). Among healthy control subjects, MCs did not express CD25. Among control subjects with IBD, CD25 expression was negative or very low ($n = 6/17$) or irregularly positive ($n = 12/17$), with an MC/inflammatory cell ratio always in favor of inflammatory cells. WT *c-Kit* was correlated to the absence of CD25 in most cases ($n = 4/6$ [67%]), whereas when the D816V *c-Kit* mutation was present, the CD25 measurement was positive in 89% of cases in which it was performed.

DISCUSSION

This study of 83 patients with mastocytosis is the largest ever to be performed for gastrointestinal manifestations in these patients. The high frequency of disabling gastrointestinal symptoms (59%)

that was observed in patients with mastocytosis is in agreement with previous reports.^{23,24} Thus gastrointestinal symptoms are as frequent as pruritus in patients with mastocytosis. Moreover, these gastrointestinal manifestations have important repercussions because they are associated with a diminished quality of life, which is again in agreement with previous studies with smaller sample sizes.^{14,24,25} The most frequent symptoms were diarrhea and bloating, followed by nausea and abdominal pain. Vomiting was reported in less than 10% of the patients. These occurrences of gastrointestinal symptoms are in accordance with previous reports.^{15,23,24,26} In addition to the association between WT *c-Kit* and high numbers of liquid stools, D816V *c-Kit* mutation, tryptase level, and gastrointestinal tract MC infiltration were not clearly associated with gastrointestinal symptoms.

In the current study we confirmed previous data showing that patients with mastocytosis were more at risk of gastroduodenal ulcers.^{8,14,15,23,24} This higher risk is classically explained by increased histamine production leading to increased gastric acid secretion.^{23,27} This mechanism is supported by several publications in patients with MC leukemia in which gastroduodenal ulcers are frequent: in this rare but severe form of mastocytosis, there is a massive MC tissue infiltration leading to high histamine liberation that could explain the ulcer formation.²⁸

Apart from an inverse trend between D816V mutation and a high diarrhea score, no association between any gastrointestinal symptoms and either D816V mutation or increased tryptase levels were observed, confirming that these 2 parameters are unrelated to disability in patients with mastocytosis.¹⁰ We hypothesize that in the absence of D816V *c-Kit* mutations but the presence of other *c-Kit* mutations, such as exon 9 or 10 mutations, or WT *c-Kit*, the

disease could be locally more invasive and induce more diarrhea. Such a phenomenon has been previously observed in patients with MC leukemia without D816V *c-Kit* mutations.²⁸⁻³¹

Furthermore, our data also confirm the results of a previous study⁷ showing that occurrence of gastrointestinal symptoms does not differ according to the age of mastocytosis onset.

Other than the histologic part of this study being one of the largest ever performed for mastocytosis, its strength lies in the comparative analysis of pathologic findings with clinical parameters. We observed histologic specificities in patients with mastocytosis, such as the presence of MC aggregates, a specific topography of MCs, and aberrant CD25-expressing MCs. However, these features were inconstant and in some cases infrequent. We also observed nonspecific lesions, such as partial villous atrophy and a mild inflammatory infiltrate associated with MCs, but the MC/inflammatory infiltrate ratio was always in favor of MCs in patients with mastocytosis, a feature already described for mastocytosis.³²⁻³⁶ Interestingly, in the control group of patients with IBD, in whom MC numbers can also be increased, the MC/inflammatory cell ratio was in favor of inflammatory cells. Previously published data regarding gastrointestinal lesions in patients with SM are conflicting. Siegert et al³⁷ did not observe any MC aggregate or aberrant CD25-expressing MCs in biopsy specimens from patients with mastocytosis, whereas Hahn and Nornick²⁰ showed an increased MC density with aberrant CD25 expression in patients with SM. We did not find any correlation between MC infiltration and gastrointestinal symptoms. These results suggest that gastrointestinal manifestations are, at least in part, related to release of MC mediators, such as histamine²³ or prostaglandin D₂.³⁸ However, direct involvement of the gastrointestinal tract by neoplastic MC proliferation has been described and could also play a role in the gastrointestinal symptoms of some patients.³⁹⁻⁴²

The high association between SM and CD25⁺ MC expression could suggest looking for mastocytosis when a patient initially presents with digestive features, especially without cutaneous manifestations, by using molecular biology.

Interestingly, CD25[−] patients (n = 4) harbored no *c-Kit* mutation, whereas CD25 was almost always positive if the D816V *c-Kit* mutation was present. Indeed, patients without the D816V *c-Kit* mutation who were CD25[−] should be investigated to verify the diagnosis of mastocytosis or determine whether it can be an MC activation syndrome.⁴³

In conclusion, disabling gastrointestinal symptoms in patients with mastocytosis are highly prevalent (ie, 59% in this study). They are not specific, and although most of the time they are not life-threatening by themselves, they do have a major functional effect on the patient. Gastrointestinal symptoms should thus be looked for and actively treated in patients with mastocytosis. Moreover, in the absence of other systemic manifestations (dermatologic manifestations can be absent in 50% of cases of SM¹⁵), such symptoms can be compatible with inflammatory bowel syndromes.⁴⁴ These kinds of patients with severe symptoms, even compatible with those seen in patients with inflammatory bowel syndromes, often undergo biological, radiologic, and endoscopic explorations. Although there are no official guidelines, it could be relevant to perform serum tryptase measurement and immunochemistry targeting MCs on gastrointestinal tract biopsy specimens in corroboration with the biological and morphological explorations usually done in this setting. This approach could adjust the diagnosis in some cases.

We thank the following physicians for collecting patient data: Drs M. Blanc (Chambéry), H. Coignard (Paris), D. Bordessoule (Limoges), X. Chanteclerc (Nancy), O. Cogel (Bordeaux), X. Guennoc (Toulon), G. Guillet (Poitiers), C. Hoarau (Tours), X. Maisonneuve (La Roche sur Yon), and C. Roux-Serratrice (Marseille). We also thank C. Baude, A.-F. Bellais, I. Hirsch, and K. Hanssens for their technical help.

Clinical implications: The gastrointestinal manifestations in patients with mastocytosis are highly prevalent and often disabling. Clinical symptoms do not correlate with histologic findings, are nonspecific, and can simulate an irritable bowel syndrome.

REFERENCES

- Valent P, Akin C, Escribano L, Föding M, Hartmann K, Brockow K, et al. Standards and standardization in mastocytosis: consensus statements on diagnostics, treatment recommendations and response criteria. *Eur J Clin Invest* 2007;37:435-53.
- Valent P, Horny HP, Escribano L, Longley BJ, Li CY, Schwartz LB, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001;25:603-25.
- Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H et al. WHO classification of tumour of haematopoietic and lymphoid tissues. 4th ed. Lyon: International agency for research on cancer; 2008.
- Valent P, Akin C, Sperr WR, Horny H-P, Arock M, Lechner K, et al. Diagnosis and treatment of systemic mastocytosis: state of the art. *Br J Haematol* 2003;122:695-717.
- Garcia-Montero AC, Jara-Acevedo M, Teodosio C, Sanchez ML, Nunez R, Prados A, et al. KIT mutation in mast cells and other bone marrow hematopoietic cell lineages in systemic mast cell disorders: a prospective study of the Spanish Network on Mastocytosis (REMA) in a series of 113 patients. *Blood* 2006;108:2366-72.
- Gupta R, Bain BJ, Knight CL. Cytogenetic and molecular genetic abnormalities in systemic mastocytosis. *Acta Haematol* 2002;107:123-8.
- Lanternier F, Cohen-Akenine A, Palmerini F, Feger F, Yang Y, Zermati Y, et al. Phenotypic and genotypic characteristics of mastocytosis according to the age of onset. *PLoS One* 2008;3:e1906.
- Travis WD, Li CY, Bergstralh EJ, Yam LT, Sweet RG. Systemic mast cell disease. Analysis of 58 cases and literature review. *Medicine (Baltimore)* 1988;67:345-68.
- Lim K-H, Tefferi A, Lasho TL, Finke C, Patnaik M, Butterfield JH, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood* 2009;113:5727-36.
- Hermine O, Lortholary O, Leventhal PS, Catteau A, Soppelsa F, Baude C, et al. Case-control cohort study of patients' perceptions of disability in mastocytosis. *PLoS One* 2008;3:e2266.
- Demis DJ, Walton MD, Higdon RS. Histaminuria in urticaria pigmentosa. A clinical study and review of recent literature with definition of the mastocytosis syndrome. *Arch Dermatol* 1961;83:127-38.
- Demis DJ. The mastocytosis syndrome: clinical and biological studies. *Ann Intern Med* 1963;59:194-206.
- Graner G, Olafsson JH, Roupe G. Studies on histamine metabolism in mastocytosis. *J Invest Dermatol* 1983;80:410-6.
- Horan RF, Sheffer AL, Austen KF. Cromolyn sodium in the management of systemic mastocytosis. *J Allergy Clin Immunol* 1990;85:852-5.
- Jensen RT. Gastrointestinal abnormalities and involvement in systemic mastocytosis. *Hematol Oncol Clin North Am* 2000;14:579-623.
- Parwaresch MR, Horny HP, Lennert K. Tissue mast cells in health and disease. *Pathol Res Pract* 1985;179:439-61.
- Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatr* 1960;23:56-62.
- Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365-76.
- Bodemer C, Hermine O, Palmérini F, Yang Y, Grandpeix-Guyodo C, Leventhal PS, et al. Pediatric mastocytosis is a clonal disease associated with D816V and other activating c-KIT mutations. *J Invest Dermatol* 2010;130:804-15.
- Hahn HP, Hornick JL. Immunoreactivity for CD25 in gastrointestinal mucosal mast cells is specific for systemic mastocytosis. *Am J Surg Pathol* 2007;31:1669-76.
- Schwartz LB, Bradford TR, Rouse C, Irani AM, Rasp G, Van der Zwan JK, et al. Development of a new, more sensitive immunoassay for human tryptase: use in systemic anaphylaxis. *J Clin Immunol* 1994;14:190-204.

22. Sperr WR, Jordan JH, Baghestanian M, Kiener HP, Samorapoompichit P, Semper H, et al. Expression of mast cell tryptase by myeloblasts in a group of patients with acute myeloid leukemia. *Blood* 2001;98:2200-9.
23. Cherner JA, Jensen RT, Dubois A, O'Dorisio TM, Gardner JD, Metcalfe DD. Gastrointestinal dysfunction in systemic mastocytosis. A prospective study. *Gastroenterology* 1988;95:657-67.
24. Horan RF, Austen KF. Systemic mastocytosis: retrospective review of a decade's clinical experience at the Brigham and Women's Hospital. *J Invest Dermatol* 1991;96(supl):5S-14S.
25. Tebbe B, Stavropoulos PG, Krasagakis K, Orfanos CE. Cutaneous mastocytosis in adults. evaluation of 14 patients with respect to systemic disease manifestations. *Dermatology* 1998;197:101-8.
26. Kirsch R, Geboes K, Shepherd NA, De Hertogh G, Di Nicola N, Lebel S, et al. Systemic mastocytosis involving the gastrointestinal tract: clinicopathologic and molecular study of five cases. *Mod Pathol* 2008;21:1508-16.
27. Friedman BS, Steinberg SC, Meggs WJ, Kaliner MA, Frieri M, Metcalfe DD. Analysis of plasma histamine levels in patients with mast cell disorders. *Am J Med* 1989;87:649-54.
28. Georgin-Lavialle S, Lhermitte L, Dubreuil P, Chandesris MO, Hermine O, Damaj G. Mast cell leukemia. *Blood* 2013;121:1285-95.
29. Georgin-Lavialle S, Lhermitte L, Suarez F, Yang Y, Letard S, Hanssens K, et al. Mast cell leukemia: identification of a new c-Kit mutation, dup(501-502), and response to masitinib, a c-Kit tyrosine kinase inhibitor. *Eur J Haematol* 2012;89:47-52.
30. Joris M, Georgin-Lavialle S, Chandesris M-O, Lhermitte L, Claisse J-F, Canioni D, et al. Mast cell leukaemia: c-KIT mutations are not always positive. *Case Report Hematol* 2012;2012:517546.
31. Krauth MT, Födinger M, Rebuzzi L, Greul R, Chott A, Valent P. Aggressive systemic mastocytosis with sarcoma-like growth in the skeleton, leukemic progression, and partial loss of mast cell differentiation antigens. *Haematologica* 2007;92:e126-9.
32. Braverman DZ, Dollberg L, Shiner M. Clinical, histological, and electron microscopic study of mast cell disease of the small bowel. *Am J Gastroenterol* 1985;80:30-7.
33. Bredfeldt JE, O'Laughlin JC, Durham JB, Blessing LD. Malabsorption and gastric hyperacidity in systemic mastocytosis. Results of cimetidine therapy. *Am J Gastroenterol* 1980;74:133-7.
34. Dantzig PI. Tetany, malabsorption, and mastocytosis. *Arch Intern Med* 1975;135:1514-8.
35. Fishman RS, Fleming CR, Li CY. Systemic mastocytosis with review of gastrointestinal manifestations. *Mayo Clin Proc* 1979;54:51-4.
36. Scott BB, Hardy GJ, Losowsky MS. Involvement of the small intestine in systemic mast cell disease. *Gut* 1975;16:918-24.
37. Siegert SI, Diebold J, Ludolph-Hauser D, Löhrs U. Are gastrointestinal mucosal mast cells increased in patients with systemic mastocytosis? *Am J Clin Pathol* 2004;122:560-5.
38. Awad JA, Morrow JD, Roberts LJ 2nd. Detection of the major urinary metabolite of prostaglandin D2 in the circulation: demonstration of elevated levels in patients with disorders of systemic mast cell activation. *J Allergy Clin Immunol* 1994;93:817-24.
39. Poynard T, Nataf C, Messing B, Modigliani R, Lecompte T, Nicolas P, et al. Secretory diarrhea and prostaglandin D2 overproduction in systemic mastocytosis. *N Engl J Med* 1982;307:186.
40. Bedeir A, Jukic DM, Wang L, Mullady DK, Regueiro M, Krasinskas AM. Systemic mastocytosis mimicking inflammatory bowel disease: a case report and discussion of gastrointestinal pathology in systemic mastocytosis. *Am J Surg Pathol* 2006;30:1478-82.
41. Scolapio JS, Wolfe J 3rd, Malavet P, Woodward TA. Endoscopic findings in systemic mastocytosis. *Gastrointest Endosc* 1996;44:608-10.
42. Takasaki Y, Tsukasaki K, Jubashi T, Tomonaga M, Kamiyama S, Makiyama K. Systemic mastocytosis with extensive polypoid lesions in the intestines; successful treatment with interferon-alpha. *Intern Med* 1998;37:484-8.
43. Hamilton MJ, Hornick JL, Akin C, Castells MC, Greenberger NJ. Mast cell activation syndrome: a newly recognized disorder with systemic clinical manifestations. *J Allergy Clin Immunol* 2011;128:147-52.e2.
44. Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology* 2006;130:1377-90.

Identification number:
Date of birth:
Sex:

1°) Do you have personal history of:

- Crohn's disease:	yes ☐	no ☐
- Ulcerative colitis:	yes ☐	no ☐
- Coeliac disease:	yes ☐	no ☐
- Gastric ulcer:	yes ☐	no ☐
- Duodenal ulcer:	yes ☐	no ☐
- hemorrhoids	yes ☐	no ☐
- Colonic polyps:	yes ☐	no ☐
- Colon cancer:	yes ☐	no ☐

2°) Do you have familial history of

- Crohn's disease:	yes ☐	no ☐
- Ulcerative colitis:	yes ☐	no ☐
- Coeliac disease:	yes ☐	no ☐
- Gastric ulcer:	yes ☐	no ☐
- Duodenal ulcer:	yes ☐	no ☐
- Colonic polyps:	yes ☐	no ☐
- Colon cancer:	yes ☐	no ☐

If you answer yes : give your parental link with the sick subject :

3°) Do you have gastro-intestinal symptoms?

Value from 0 to 10 the intensity of your symptoms.

Encircle your answer (0 = no symptoms, 10 = frequent and disabling symptoms)

- Bloating, aerophagia, belching:	0 1 2 3 4 5 6 7 8 9 10
- Abdominal pain:	0 1 2 3 4 5 6 7 8 9 10

How often have you experienced the following symptoms each day of the last week?

- Nausea:	D1:..... D2:..... D3:..... D4:..... D5:..... D6:..... D7:.....
- Vomiting:	D1:..... D2:..... D3:..... D4:..... D5:..... D6:..... D7:.....
- Liquid stools:	D1:..... D2:..... D3:..... D4:..... D5:..... D6:..... D7:.....

Did you ever observed blood in your stools: yes ☐ no ☐

4°) Did you have the following examinations:

- Upper gastro-intestinal tract endoscopy:	yes ☐	no ☐
(Examination of the oesophagus and the stomach)		
- Coloscopy (Examination of the colon):	yes ☐	no ☐

5°) What medication do you take regularly for your gastro-intestinal symptoms?

FIG E1. Gastrointestinal symptoms and history questionnaire.

TABLE E1. Main features of the 83 patients with mastocytosis

Patient	Age on study (y)	Sex	c-Kit sequencing	Valent stage	Tryptase ($\mu\text{g/L}$)
1	57	F	D816V	CM	8.2
2	46	F	D816V	CM	7
3	60	M	NA	CM	13.9
4	50	M	D816V	CM	13.1
5	51	F	WT	CM	5.9
6	53	F	WT	CM	5.8
7	25	M	WT	CM	11
8	47	F	NA	CM	7
9	47	M	WT	CM	5.3
10	30	F	D816V	CM	9.5
11	33	F	D816V	CM	5.3
12	47	F	NA	CM	NA
13	64	F	D816V	CM	18.5
14	58	F	D816V	CM	22.9
15	59	F	D816V	CM	1.41
16	34	F	D816V	CM	1
17	44	F	D816V	CM	11.3
18	64	M	D816V	CM	23.2
19	54	F	D816V	ISM	18
20	44	M	D816V	ISM	36.4
21	42	F	D816V	ISM	18
22	62	F	D816V	ISM	15.7
23	59	F	D816V	ISM	428
24	66	F	D816V	ISM	NA
25	75	F	D816V	ISM	9.3
26	39	F	D816V	ISM	356
27	33	F	WT	ISM	3.6
28	48	F	NA	ISM	7.9
29	51	M	D816V	ISM	47.7
30	39	F	D816V	ISM	68
31	64	F	D816V	ISM	81.7
32	50	F	D816V	ISM	153
33	59	F	D816V	ISM	NA
34	44	F	D816V	ISM	42
35	50	F	WT	ISM	200
36	72	M	D816V	ISM	33.8
37	45	F	WT	ISM	14
38	51	F	D816V	ISM	17
39	32	F	D816V	ISM	6.6
40	62	M	D816V	ISM	36.1
41	55	F	D816V	ISM	22
42	65	M	D816V	ISM	40.4
43	30	F	NA	ISM	41.8
44	47	F	D816V	ISM	177
45	65	F	D816V	ISM	257
46	57	M	D816V	ISM	228
47	41	F	WT	ISM	13.5
48	51	M	D816V	ISM	13.9
49	38	F	D816V	ISM	25
50	41	F	D816V	ISM	79
51	57	F	D816V	ISM	86.5
52	53	M	D816V	ISM	17.7
53	58	F	D816V	ISM	46.7
54	70	M	D816V	ISM	15
55	45	M	D816V	ISM	24.2
56	62	M	WT	ISM	NA
57	69	F	WT	ISM	48
58	67	F	D816V	ISM	20.8
59	46	F	D816V	ISM	3.1
60	50	M	D816V	ISM	91.6

(Continued)

TABLE E1. (Continued)

Patient	Age on study (y)	Sex	c-Kit sequencing	Valent stage	Tryptase ($\mu\text{g/L}$)
61	43	F	D816V	ISM	11.4
62	80	F	D816V	ISM	97
63	46	M	D816V	ISM	28
64	60	F	D816V	ISM	129
65	63	F	D816V	ISM	57.7
66	60	F	D816V	ISM	31.4
67	44	F	D816V	ISM	62
68	38	F	D816V	ISM	21
69	72	F	D816V	ISM	57.5
70	54	F	D816V	ISM	15
71	29	F	WT	ISM	10.1
72	69	M	WT	ISM	23.6
73	47	M	D816V	ISM	252
74	64	F	D816V	ISM	35.6
75	50	M	D816V	ISM	55.9
76	40	F	WT	SM-AHNMD	7.81
77	51	F	D816V	ASM	334
78	84	M	WT	ASM	273
79	57	F	D816V	ASM	37.4
80	27	M	D816V	ASM	570
81	40	M	D816V	ASM	200
82	38	F	WT	ASM	95
83	84	F	D816V	ASM	1828

ASM, Aggressive systemic mastocytosis; CM, cutaneous mastocytosis; F, female; ISM, indolent systemic mastocytosis; M, male; NA, not available; SM-AHNMD, systemic mastocytosis with an associated clonal hematologic non-MC lineage disease.

TABLE E2. Gastrointestinal symptoms according to MC topography (scattered vs localized) in patients with mastocytosis: stomach, duodenum, ileum, and rectum and colon

	Scattered	Localized	P value
Stomach			
No.	13	4	
Gastroduodenal ulcer history	9.1% (1)	75% (3)	.033
Bloating score, mean $\pm$ SEM	5.3 $\pm$ 1.3	5.5 $\pm$ 1.2	.89
Bloating score ≥ 5 , % (no.)	44.4% (4)	33.3% (1)	1
Abdominal pain score, mean $\pm$ SEM	4.7 $\pm$ 1.1	5.0 $\pm$ 2.1	.84
Abdominal pain score ≥ 5 , % (no.)	55.6%	33.3% (1)	1
Nausea score, mean $\pm$ SEM	19.3 $\pm$ 6.9	0.25 $\pm$ 0.25	.066
Nausea ≥ 1 , % (no.)	70% (7)	25% (1)	.24
Vomiting score ≥ 1 , % (no.)	20% (2)	0%	1
Diarrhea score, mean $\pm$ SEM	14.7 $\pm$ 3.5	2.3 $\pm$ 0.5	.026
Diarrhea score ≥ 5 , % (no.)	72.7% (8)	0%	.026
<i>c-Kit</i> mutation, % (no.)	50% (6)	100% (4)	.22
Tryptase level, mean $\pm$ SEM	63.4 $\pm$ 32.0	100.9 $\pm$ 53.1	.09
Tryptase level >20 mg/L, % (no.)	41.7% (5)	100% (4)	.09
Duodenum			
No.	5	11	
Gastroduodenal ulcer history	0%	20%	1
Bloating score, mean $\pm$ SEM	5.0 $\pm$ 2.0	3.8 $\pm$ 1.3	.53
Bloating score ≥ 5 , % (no.)	33.3% (1)	28.6% (2)	1
Abdominal pain score, mean $\pm$ SEM	5.8 $\pm$ 1.4	2.6 $\pm$ 1.3	.13
Abdominal pain score ≥ 5 , % (no.)	100% (3)	14.3% (1)	.03
Nausea score, mean $\pm$ SEM	12.0 $\pm$ 6.1	9.7 $\pm$ 4.7	.55
Nausea score ≥ 1 , % (no.)	66.7% (2)	44.4% (4)	1
Vomiting score ≥ 1 , % (no.)	33.3% (1)	11.1% (1)	.45
Diarrhea score, mean $\pm$ SEM	8.8 $\pm$ 4.1	12.3 $\pm$ 4.2	.72
Diarrhea score ≥ 5 , % (no.)	50% (2)	50% (5)	1
<i>c-Kit</i> mutation, % (no.)	66.7% (2)	60% (6)	1
Tryptase level, mean $\pm$ SEM	11.2 $\pm$ 3.0	79.1 $\pm$ 33.9	.12
Tryptase level >20 mg/L, % (no.)	0%	63.6% (7)	.077
Ileum			
No.	3	6	
Bloating score, mean $\pm$ SEM	3.7 $\pm$ 1.3	5.0 $\pm$ 2.4	.7
Bloating score ≥ 5 , % (no.)	0	50% (2)	.47
Abdominal pain score, mean $\pm$ SEM	2.7 $\pm$ 1.8	3.3 $\pm$ 2.4	1
Abdominal pain score ≥ 5 , % (no.)	50% (1)	25% (1)	1
Nausea score, mean $\pm$ SEM	8.0 $\pm$ 8.0	16.5 $\pm$ 9.6	.62
Nausea score ≥ 1 , % (no.)	50% (1)	50% (2)	1
Vomiting score ≥ 1 , % (no.)	0%	0%	NA
Diarrhea score, mean $\pm$ SEM	10.3 $\pm$ 5.4	11.2 $\pm$ 4.0	.65
Diarrhea score ≥ 5 , % (no.)	66.7% (2)	60% (3)	1
<i>c-Kit</i> mutation, % (no.)	100% (3)	75% (3)	1
Tryptase level, mean $\pm$ SEM	20.6 $\pm$ 13.8	95.9 $\pm$ 65.3	.18
Tryptase level >20 mg/L, % (no.)	33.3% (1)	80% (3)	.46
Rectum and colon			
No.	5	9	
Bloating score, mean $\pm$ SEM	6.0 $\pm$ 2.0	4.1 $\pm$ 1.4	.39
Bloating score ≥ 5 , % (no.)	66.7% (2)	33.3% (3)	.52
Abdominal pain score, mean $\pm$ SEM	4.5 $\pm$ 2.2	2.7 $\pm$ 1.2	.49
Abdominal pain score ≥ 5 , % (no.)	66.7% (2)	33.3% (3)	.52
Nausea score, mean $\pm$ SEM	29.3 $\pm$ 15.0	7.0 $\pm$ 5.7	.17
Nausea score ≥ 1 , % (no.)	75% (3)	33.3% (3)	.52
Vomiting score ≥ 1 , % (no.)	0%	0%	NA
Diarrhea score, mean $\pm$ SEM	11.8 $\pm$ 4.3	13.1 $\pm$ 4.8	.86
Diarrhea score ≥ 5 , % (no.)	75% (3)	62.5% (5)	1
<i>c-Kit</i> mutation, % (no.)	33.3% (1)	100% (7)	.067
Tryptase level, mean $\pm$ SEM	20.3 $\pm$ 10.4	135.8 $\pm$ 53.4	.089
Tryptase level >20 mg/L, % (no.)	50% (2)	71.4% (5)	.58

NA, Not available. Statistical significance is indicated with boldface.