MAST CELL DISORDERS OF THE GI TRACT

Gert De Hertogh
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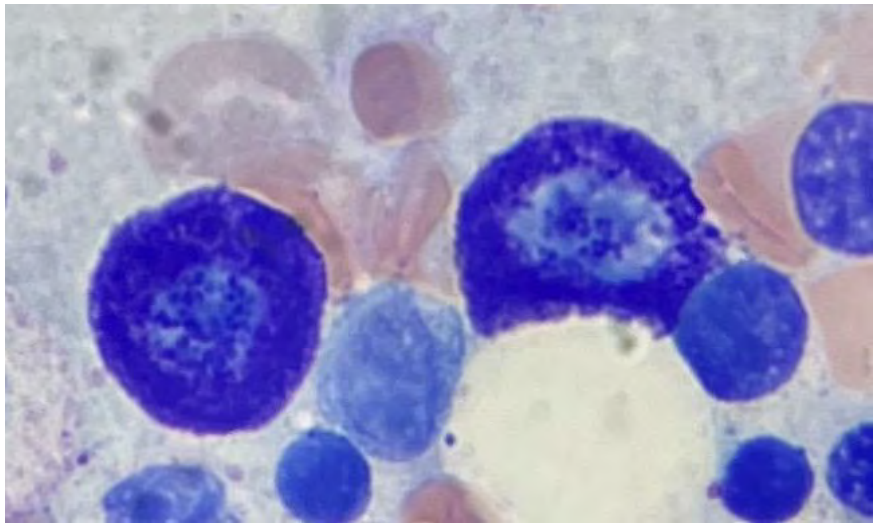
Introduction (1)

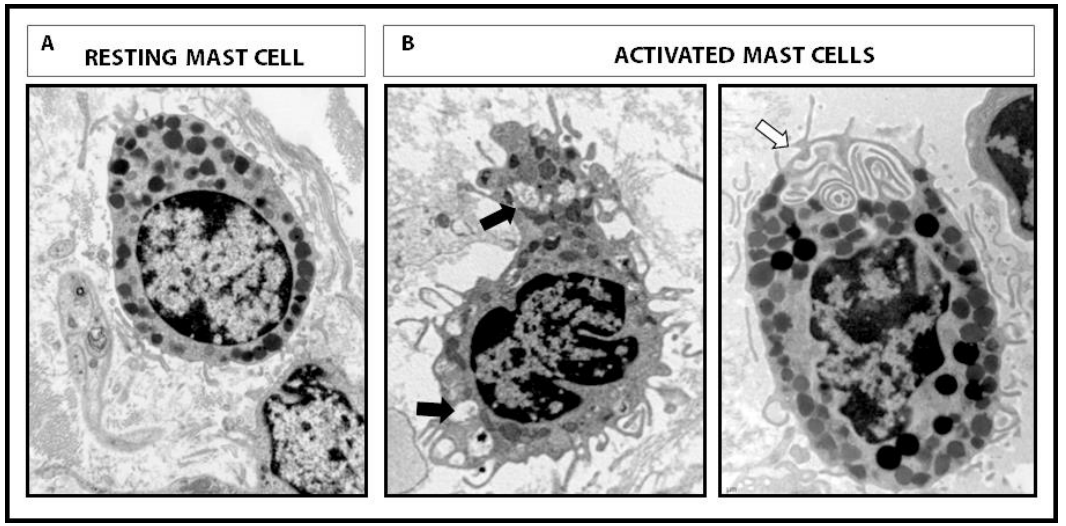
- Mast cells are derived from hematopoietic stem cells
- Circulating mast cell progenitors → all vascularised tissues
- Mainly at interfaces (skin, GI, respiratory, urinary)
- Intestinal homing via α4β7 integrin
- Further differentiation & maturation according to local needs
- Classification based on protease content:
  - Tryptase > chymase: mucosal
  - Tryptase & chymase: submucosal

Introduction (2)

- Granulated immune cell
- Receptors for immune ligands (Fc IgE, …) & mediators (neurotransmitters, …)
- Activation → degranulation → release of biologically active products (tryptase, histamine, heparin, …)



Two mast cells in bone marrow at 1000x (Wright's stain). Vortioxetine, CC BY-SA 4.0, via Wikimedia Commons



EM x 12000
PMID: 30744042

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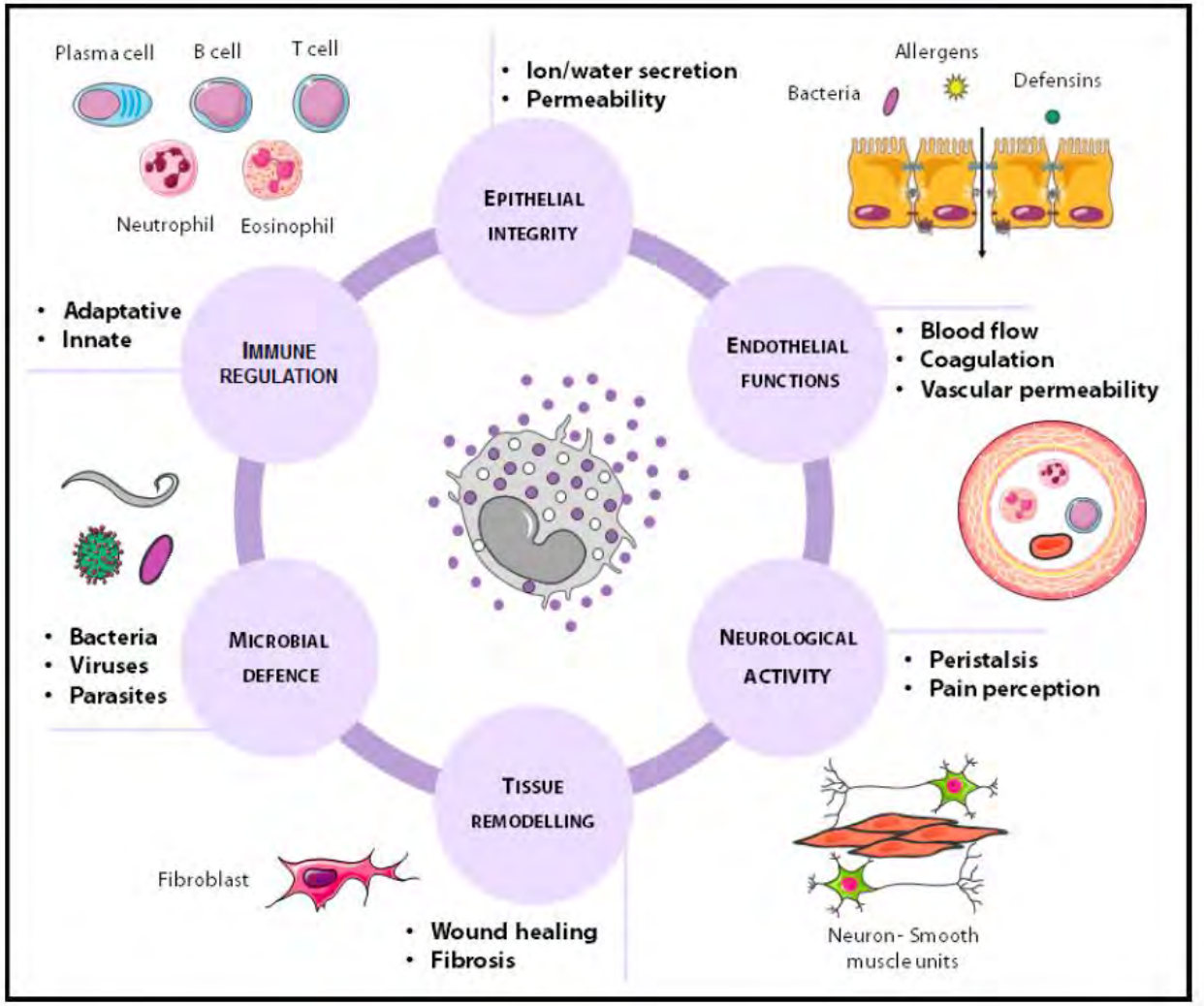
Functions of mast cells in the GI tract



PMID: 30744042

Role of mast cells in digestive diseases

- Food allergies (IgE & non-IgE mediated)
- Chronic urticaria
- Some forms of gastritis
- Celiac disease (↑ numbers)
- Chronic inflammatory bowel disease (↑ numbers & signs of degranulation)
- Irritable bowel syndrome
- “Mastocytic enterocolitis”
- Mast cell activation syndrome

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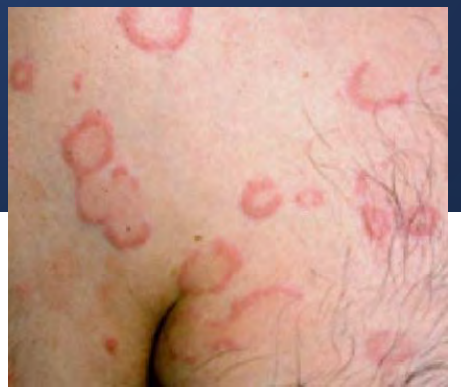
Chronic urticaria

Chronic urticaria is associated with mast cell infiltration in the gastroduodenal mucosa

Francesca Minnei · Charlotte Wetzels · Gert De Hertogh · Peter Van Eyken · Nadine Ectors · Rossano Ambu · Gavino Faa · Anne Marie Kochuyt · Karel Geboes

Virchows Arch (2006) 448: 262–268
DOI 10.1007/s00428-005-0111-3

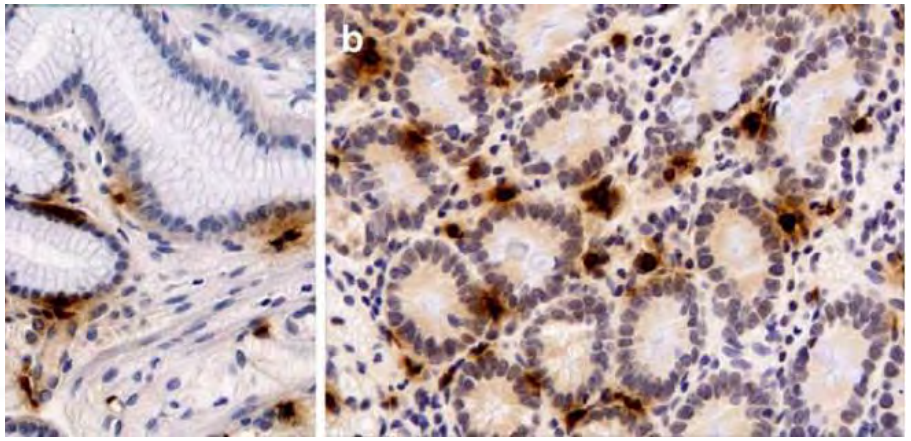


- Chronic recurrent skin eruptions, most commonly in middle-aged women
- Mast cells in skin / GI tract release vaso-active mediators after contact with (pseudo)allergenic substances (e.g. in food, medications) ?
- Numbers of tryptase+ mast cells were significantly higher in CU pts than in controls

Table 1 Mean mast cell numbers per HPF and per mm^2 in disease controls and CU patients[a]

Disease controls			CU patients		
	per HPF	per mm^2		per HPF	per mm^2
Stomach			Stomach		
All (n=20)	20.2±6.2 [17.4–22.9]	133.3±36.6 [117.3–149.4]	All (n=38)	32.4±9.4 [29.5–35.4]	186.0±46.9 [171.1–200.9]
Belgian (n=15)	20.7±6.5		All, normal[b] (n=20)	30.4±9.6 [26.2–34.6]	173.9±41.0 [155.9–191.9]
Italian (n=5)	18.4±5.3				
Duodenum			Duodenum		
All (n=35)	32.5±9.2 [29.4–35.6]	209.2±61.6 [188.8–229.6]	All (n=36)	44.8±16.9 [39.2–50.3]	246.0±89.2 [216.8–275.1]
Belgian (n=6)	32.0±10.2		All, normal[b] (n=27)	45.2±18.2 [38.4–52.1]	248.6±95.1 [212.7–284.4]
Italian (n=29)	32.6±9.2				

[a]Mean±standard deviation (95% confidence interval)
[b]Normal = biopsies histologically normal



ptase, 400x (a) stomach (b) duodenum

Gastritis (1)

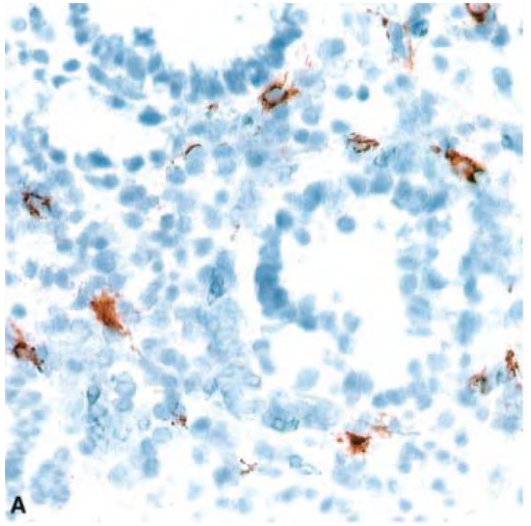
Histopathology 2003, **43**, 538–549

Mast cell chymase expression in *Helicobacter pylori*-associated gastritis

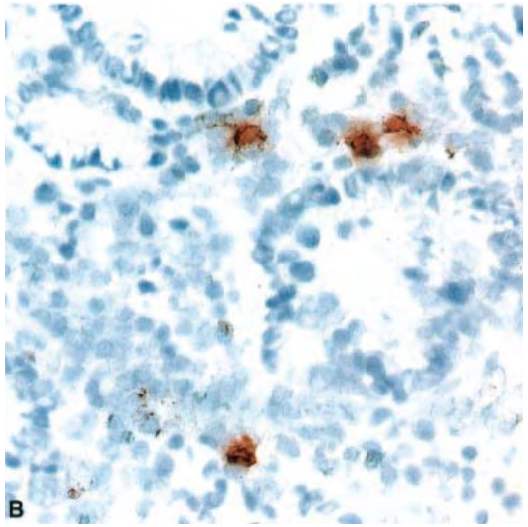
T Matsuo, Y Ikura, M Ohsawa, M Ogami, S Kayo, N Yoshimi, E Hai, T Naruko,[2] M Ohishi,[3] K Higuchi,[1] T Arakawa[1] & M Ueda

- Numbers of $MC_{T/C}$ significantly ↑ in Hp gastritis
- Correlates with accumulation of neutrophils, T-lymfocytes, macrophages
- Tryptase &/ chymase may attract neutrophils & monocytes to sites of gastric mucosal inflammation…

	Normal	Gastritis	*P*-value
Mucosal layer			
Tryptase (+) MCs (/mm^2)	27.3 ± 17.4	150.6 ± 72.5	<0.0001
Chymase (+) MCs (/mm^2)	2.0 ± 2.6	17.6 ± 14.7	<0.0001



IHC tryptase, 360x



IHC chymase, 360x

Gastritis (2)

Diagnostic Pathology

BioMed Central

Research

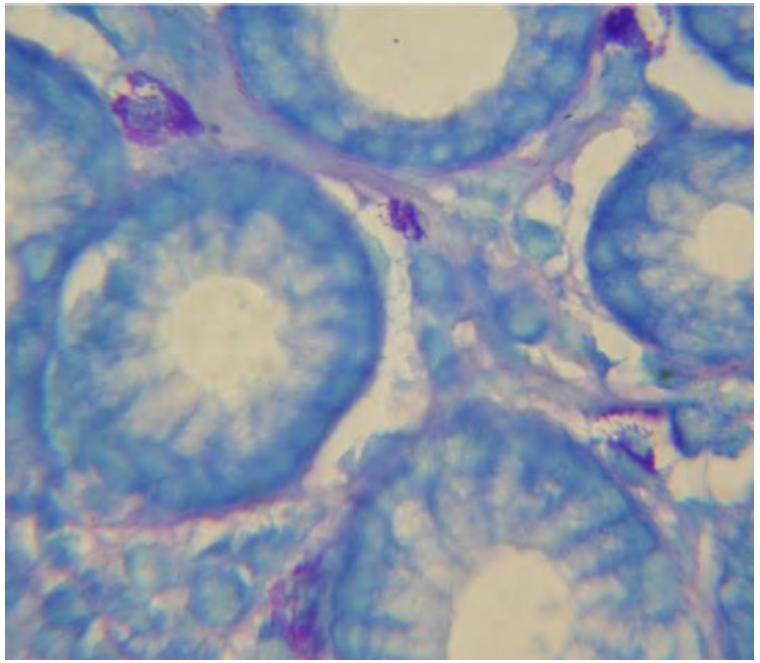
Open Access

Mast cell gastritis: Children complaining of chronic abdominal pain with histologically normal gastric mucosal biopsies except for increase in mast cells, proposing a new entity

Fatemeh E Mahjoub*[1], Fatemeh Farahmand[2], Zahra Pourpak[3], Hoda Asefi[4] and Zahra Amini[4]

Diagnostic Pathology 2009, 4:34 doi:10.1186/1746-1596-4-34

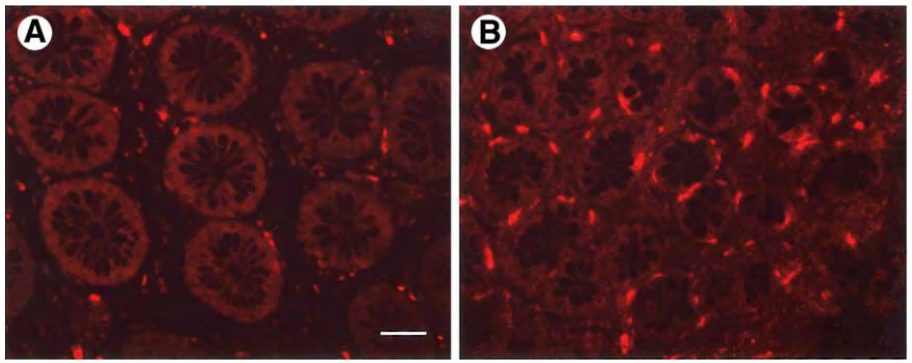
- 895 Iranian children, GI symptoms, gastroscopy
- 86/895 had ~ normal endoscopy & biopsy
- Mast cells counts:
  - Metachromatic cells on Giemsa stain
  - Evaluation at x1000 under oil immersion
- Broad distribution of mast cell numbers
  - Mean density 45,6 ± 13,8 / 0,25 mm^2
  - = far above the "normal" (12,6 ± 0,87 / 0,25 mm^2)
- **"Mast cell gastritis"**



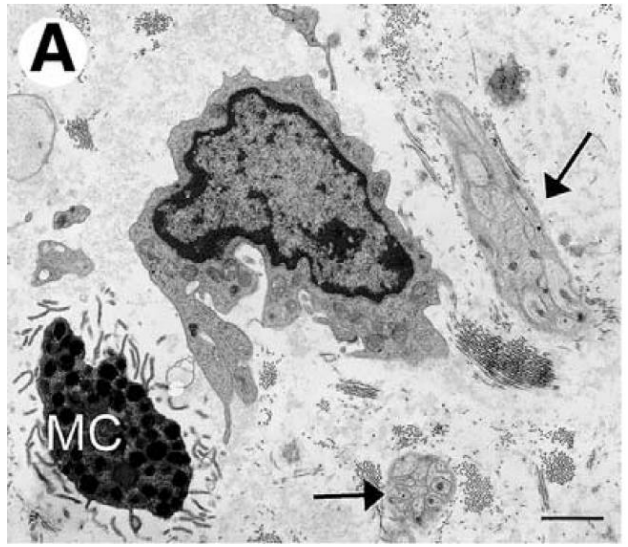
Irritable Bowel Syndrome

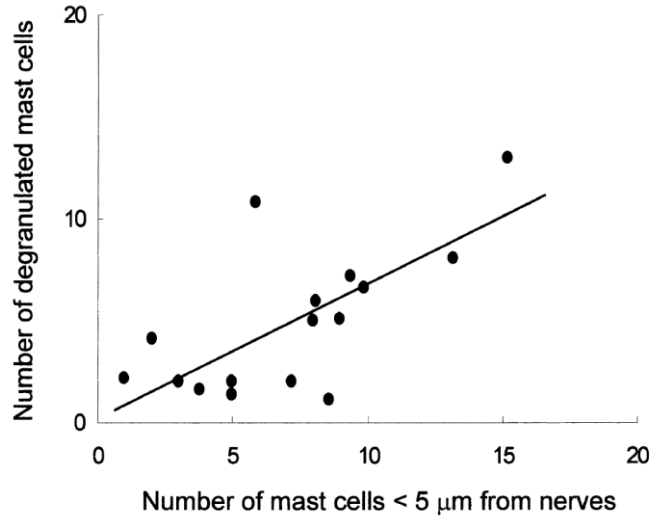
* Barbara G, Stanghellini V, De Giorgio R, et al. Gastroenterology 2004;126(3):693-702. PMID: 14988823.
* Kirsch R, Riddell RH. Mod Pathol 2006;19(12):1638-45. PMID: 17013373.

- Global, frequent, invalidating functional GI disorder
- Chronic abdominal discomfort / pain & altered bowel habits (Rome IV criteria)
- Multifactorial etiology (a.o. post-infectious)
- Mast cells:
  - ↑ numbers
  - ↑ proximity to enteric nerve endings
  - ↑ spontaneous release of tryptase & histamine
  - ↑ degranulation



IF tryptase (a) healthy control (b) IBS patient





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“Mastocytic enterocolitis”

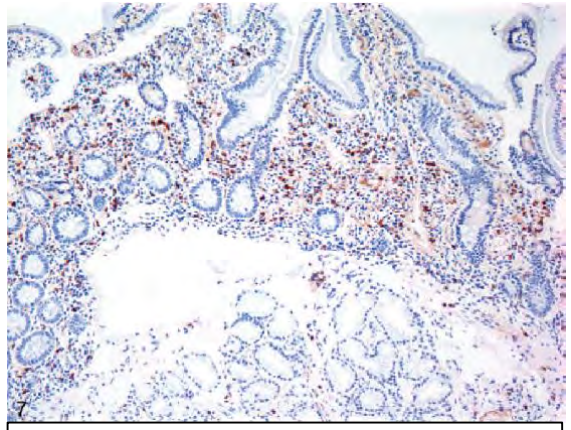
Mastocytic Enterocolitis

Increased Mucosal Mast Cells in Chronic Intractable Diarrhea

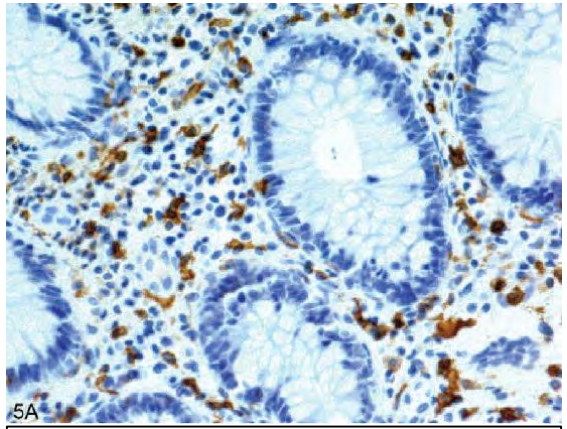
Shriram Jakate, MD, FRCPath; Mark Demeo, MD; Rohan John, MD; Mary Tobin, MD; Ali Keshavarzian, MD

(*Arch Pathol Lab Med.* 2006;130:362–367)

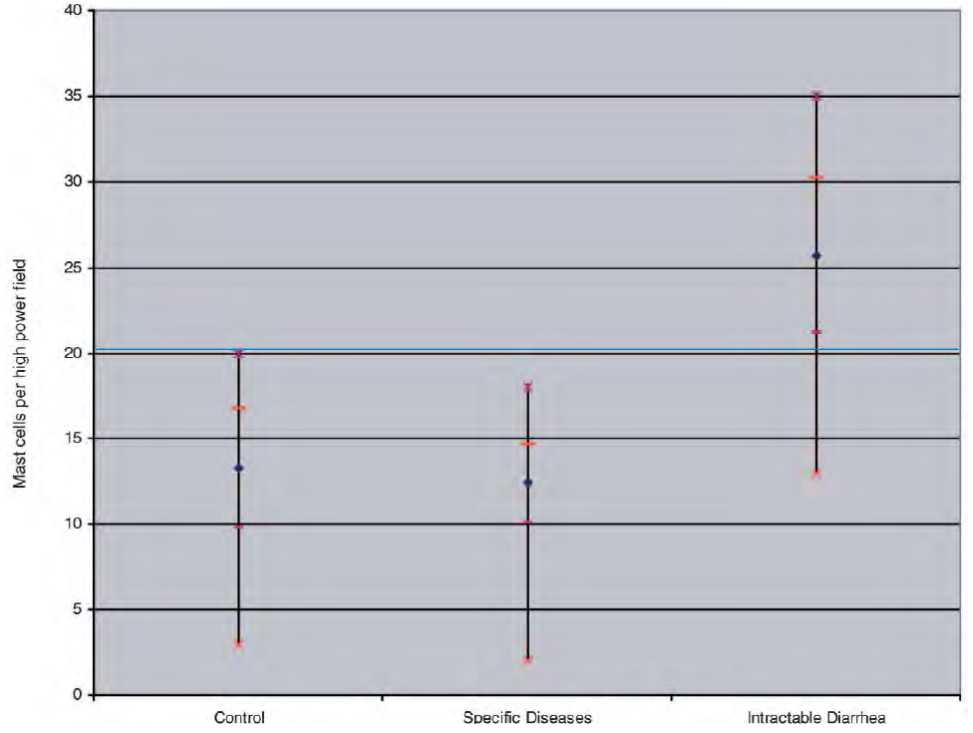
- Adult pts with chronic intractable diarrhea
- No apparent cause after exclusion of IBS, IBD, celiac disease, microscopic colitis, chronic infections, idiopathic secretory diarrhea
- Colonic / duodenal biopsies normal on HE
- ↑ mast cell numbers on tryptase stain (i.e. > 20 / HPF) in 70% of such pts
- 2/3rd of these pts respond to antihistaminica / mast cell stabilizers



IHC tryptase, x100



IHC tryptase, x400



Mast cell activation syndrome (1)

Digestive Diseases and Sciences (2021) 66:965–982
https://doi.org/10.1007/s10620-020-06264-9

REVIEW

Mast Cell Activation Syndrome: A Primer for the Gastroenterologist

Leonard B. Weinstock[1] · Laura A. Pace[2] · Ali Rezaie[3] · Lawrence B. Afrin[4] · Gerhard J. Molderings[5]

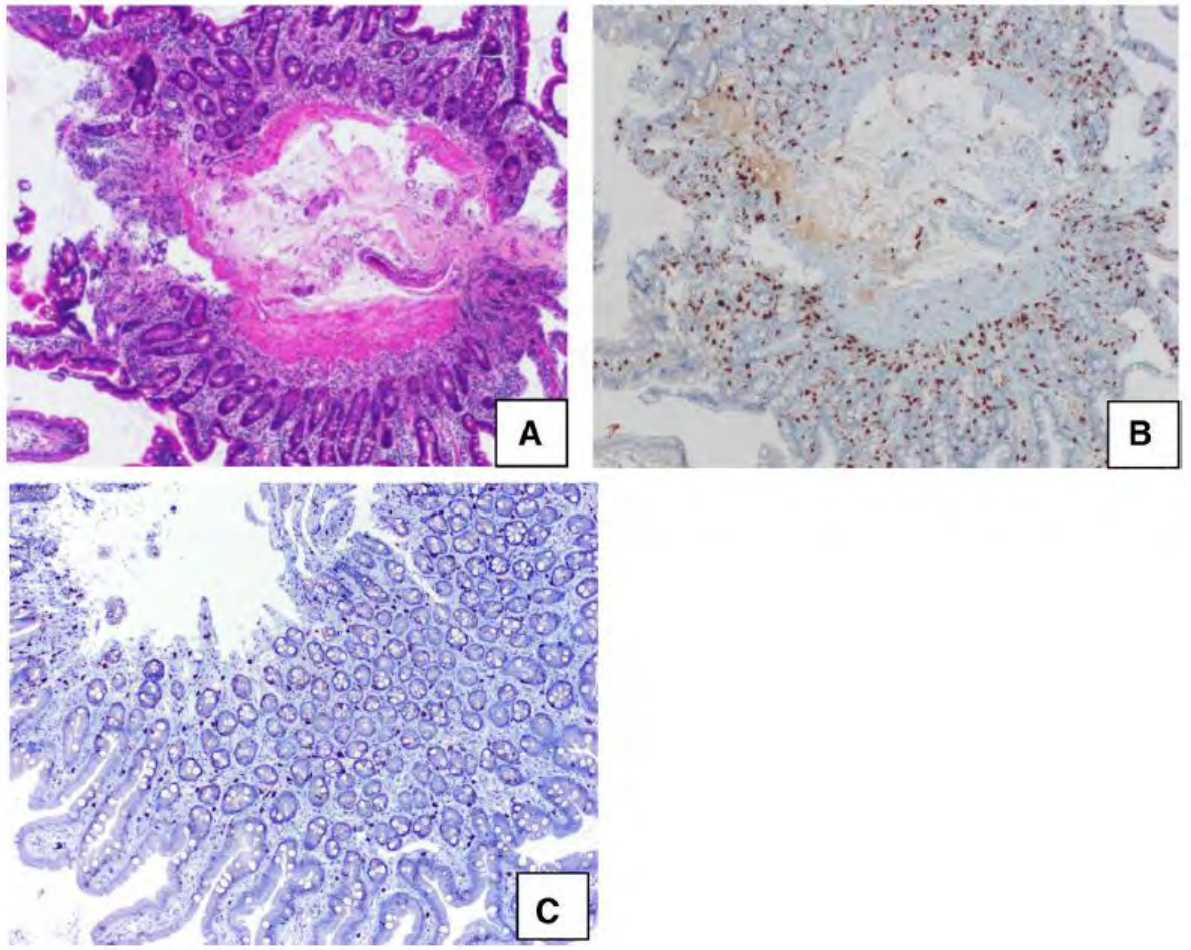
- Chronic multisystem disorder of abnormal mast cell activation, leading to inflammatory & allergic symptoms
- GI manifestations are common & may be refractory to standard therapy (DDx Irritable Bowel Syndrome)
- Due to mutations of mast cell regulatory genes ?
- GI biopsies: “only modest” ↑ in mast cell nrs (> 50 / HPF ?), no clustering, no abnormal morphology
- Bone marrow normal
- Diagnosis:
  - MAJOR : Symptoms in 2 or more systems
  - MINOR:
    - Elevated mast cell mediators in blood &/ urine
    - Clinical improvement upon mast cell-directed R/ (antihistaminica / mast cell stabilizers)
    - ≥ 20 MCs / HPF in extracutaneous tissues (luminal GI tract, bladder)

Mast cell activation syndrome (2)

Organ/system	Symptom/finding
Constitutional	Fatigue, fevers, weight loss or gain
Eyes, ears, nose, throat	Conjunctivitis, tinnitus, hearing loss, rhinitis, sinusitis, sore throat
Neurologic	Headaches, migraines, brain fog, anxiety, flushing, nausea
Cardiovascular	Chest pain, palpitations, hypotension
Urogenital	Frequency, urgency, dysuria
Esophageal	Heartburn, dysphagia, globus, chest pain
Stomach	Dyspepsia
Small and large intestine	Abdominal pain/discomfort, diarrhea, constipation
Hepatic	Elevated transaminases, hepatomegaly
Salivary glands	Swelling
Lymphatics	Lymphadenopathy
Dermatologic	Flushing, pruritus, urticaria, rashes
Musculoskeletal	Myalgia, arthralgia, edema

Table 1 Gastrointestinal symptoms in mast cell activation syndrome

Gastrointestinal symptom	Frequency (%)
Nausea ± vomiting	57
Heartburn	50
Abdominal pain	48
Atypical chest pain	40
Alternating diarrhea and constipation	36
Esophageal dysphagia	35
Oral symptoms or sores	30
Diarrhea	27
Constipation	14



(a) MCAS, HE, x100 : normal
(b) MCAS, ICH c-kit, x 100 : > 50 MCs / HPF
(c) Healthy control, ICH c-kit, x 100 : 10 MCs / HPF

Pathologists' problems !

- Mast cells are an important component of the GI mucosa
- MC "abnormalities" have been documented in several inflammatory / functional disorders with / without GI symptoms
- Pathologists may feel that they should evaluate GI biopsies for MCs
  - based on the presence of an abnormal cell infiltrate
  - based on the clinical presentation
- Clinicians request MC quantification more often than in the past

QUESTIONS

1. How can we identify mast cells ?
2. How should we count mast cells ?
3. What are the normal mast cell numbers ?
4. When is it useful to report mast cell counts ?

How can we identify mast cells ?

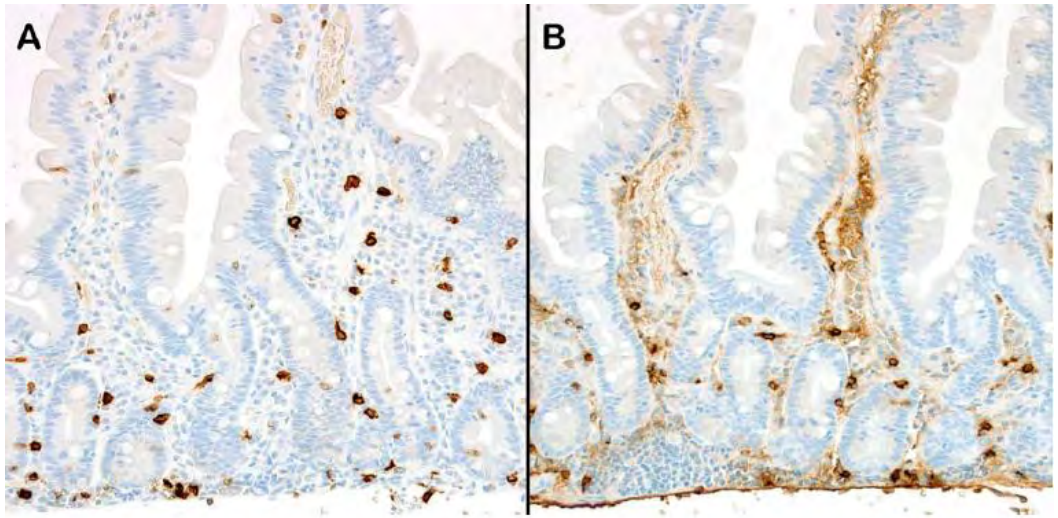
Quantification of Mucosal Mast Cells in the Gastrointestinal Tract

A Primer for Practicing Pathologists

Robert M. Genta, MD; Kevin O. Turner, DO; Margaret H. Collins, MD; Joshua B. Wechsler, MD; Nicoleta C. Arva, MD, PhD; Maria A. Pletneva, MD, PhD; Evan S. Dellon, MD, MPH; Marjorie M. Walker, BMedSci, BMBS

(*Arch Pathol Lab Med.* 2024;148:e25–e35; doi: 10.5858/arpa.2023-0070-OA)

- Metachromatic dyes (Giemsa stain, Wright's stain, toluidine blue stain)
  - >< accurate detection requires visualisation at high magnification (x1000)
  - >< accuracy depends on # of granules; partly degranulated MCs may be classified as eosinophils
- IHC for MC proteases
  - Tryptase = universal MC component
  - Chymase ≠ universal : often low amount / none in GI MCs
- IHC for CD117 (c-kit)
  - Receptor in the MC cell membrane
  - Also present in interstitial cells of Cajal and endothelial cells



IHC for (a) c-kit, (b) tryptase. x200

- C-kit stain is "cleaner" than tryptase, but less specific
- A "dirty" tryptase stain may indicate MC degranulation (??)

How should we count mast cells ?

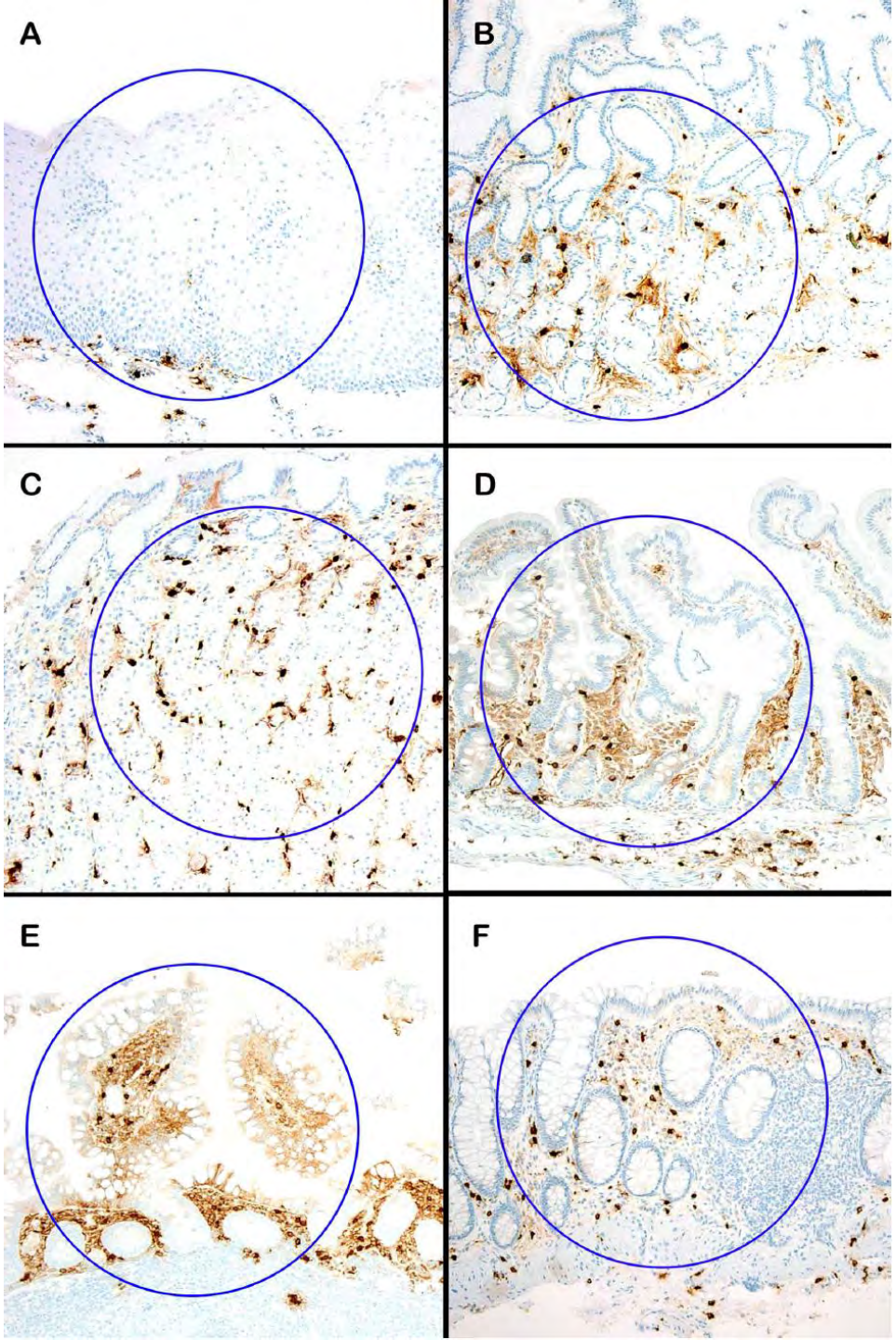
Quantification of Mucosal Mast Cells in the Gastrointestinal Tract

A Primer for Practicing Pathologists

Robert M. Genta, MD; Kevin O. Turner, DO; Margaret H. Collins, MD; Joshua B. Wechsler, MD; Nicoleta C. Arva, MD, PhD; Maria A. Pletneva, MD, PhD; Evan S. Dellon, MD, MPH; Marjorie M. Walker, BMedSci, BMBS

(*Arch Pathol Lab Med.* 2024;148:e25–e35; doi: 10.5858/arpa.2023-0070-OA)

- Avoid crushed / twisted sections
- Evaluate at low magnification (40x – 100x):
  - Select a properly oriented area (no tangential sections)
  - Only in the mucosa:
    - Not in the esophageal lamina propria
    - Not in the muscularis mucosae
    - Not in the submucosa
- Evaluate at intermediate magnification (200x):
  - MC clusters / variable MC density ?
- If no MC clusters & evenly distributed:
  - Count MCs in a set of adjacent, non-overlapping HPFs (400x)
  - Round / “elongated” cells; no loose granules; no non-nucleated cell fragments
  - Report as peak value / average in 3-5 HPFs
  - Report as MC number / mm^2 (every pathologist must do his own conversion)


A
B
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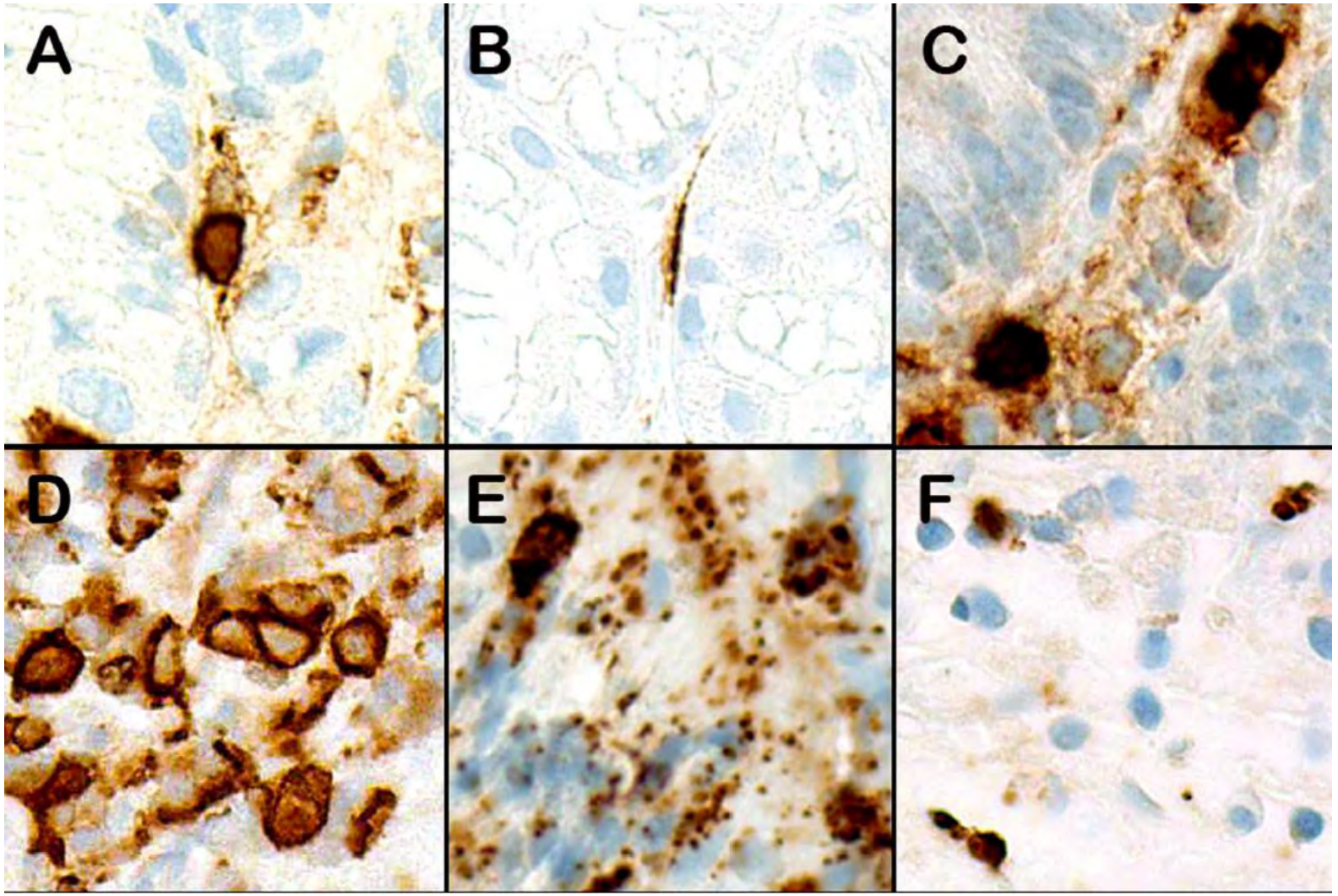
A
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What are the normal mast cell numbers ? (same ref)

Articles Reporting Mast Cell (MC) Counts in at Least 10 Healthy Individuals

Source, y	Organ	Healthy Individuals, No.	Stain Used	MC/hpf, ± SD (Range)	Age
Nielsen et al,[59] 2006	Esophagus	24	Tryp	3 (1–7)	P
Kirsch et al,[60] 2007	Esophagus	22	Tryp	0	P
Lee et al,[61] 2014	Esophagus	10	Tryp	7.6 ± 3.7	A
Strasser et al,[42] 2018	Esophagus	12	Chymase	0	A
Nakajima et al,[43] 1997	Stomach	13	Tryp	28.4 ± 3.8	A
Minnei et al,[62] 2006	Stomach	50	Tryp	20.2 ± 6.2	A
Hofman et al,[63] 2007	Stomach	48	Tryp	28.8 ± 2.2	A
Mahjoub et al,[64] 2009	Stomach	25	Giemsa	43 (30–78)	A
Singh et al,[65] 2018	Stomach	10	Tryp	12.4 ± 2.7	P
Reed et al,[16] 2021	Stomach	55	Tryp	23.4 ± 8.2	A
Jakate et al,[8] 2006	Duodenum	50	Tryp	13.2 ± 3.7	A
Minnei et al,[62] 2006	Duodenum	50	Tryp	32.5 ± 9.2	A
Yuan et al,[66] 2015	Duodenum	21	Tol blue	24.6 ± 5.0	A
Singh et al,[65] 2018	Duodenum	10	Tryp	18.2 ± 2.9	P
Reed et al,[16] 2021	Duodenum	58	Tryp	25.1 ± 8.3	A
Selbekk et al,[67] 1985	Jejunum	79	Pinacyanol	26 (5–69)	A
Guilarte et al,[68] 2007	Jejunum	14	CD117	14.3 ± 4.4	A
Martinez et al,[69] 2013	Jejunum	30	CD117	17.2 ± 8.8	A
Weston et al,[70] 1993	Ileum	15	Low-pH AB	6.8 ± 1.1	A
Jakate et al,[8] 2006	Colon	50	Tryp	13.6 ± 3.1	A
Lee et al,[71] 2008	Colon	12	Tryp	6.8 ± 2.0	A
Piche et al,[72] 2008	Colon	21	CD117	4 (3–7)	A
Saad,[73] 2011	Colon (R)	41	Tryp	15.2 ± 7.9	P
Saad,[73] 2011	Colon (L)	41	Tryp	15.2 ± 6.3	P
Braak et al,[74] 2012	Colon (R)	20	CD117	63 ± 6.2	A
Braak et al,[74] 2012	Colon (L)	20	CD117	88.1 ± 9.3	A
Ahn et al,[46] 2013	Colon	25	Tryp	12.9 ± 5.4	A
Doyle et al,[49] 2014	Colon	100	Tryp	19 ± 6.1	A
Sethi et al,[9] 2015	Colon	89	CD117	24.1 ± 8.7	A
Ahn et al,[46] 2014	Rectum	25	Tryp	22.4 ± 5.6	A

Abbreviations: A, adult; AB, Alcian blue; hpf, high-power field; L, left; P, pediatric; R, right; Tol blue, toluidine blue; Tryp, tryptase.

"IN GENERAL, COUNTS GREATER THAN 30 MAST CELLS PER HPF ARE UNUSUAL"

When is it useful to report mast cell numbers ? (1)

Mast cell evaluation in gastrointestinal biopsies: should we be counting? A critical review and practical guide for the surgical pathologist

Sameer Shivji, James Ryan Conner & Richard Kirsch
Department of Pathology & Laboratory Medicine, Mount Sinai Hospital, Toronto, ON, Canada

Histopathology 2023, 82, 960–973.

- Mast cell activation syndrome :
  - ≥ 20 MCs / HPF in GI biopsies is a minor diagnostic criterion
  - This threshold was proposed ***without peer-reviewed evidence***
  - ***Has not been validated in any controlled studies to date***, e.g. :
    - Hamilton MJ, Hornick JL, Akin C, et al. J Allergy Clin Immunol 2011;128(1):147-152. PMID: 21621255
    - Hamilton MJ, Zhao M, Giannetti MP, et al. Am J Surg Pathol 2021;45(7):997-1004. PMID: 33481382
- Chronic diarrhea without identifiable cause, aka “mastocytic enterocolitis”, aka “allergic mastocytic gastroenteritis / colitis:
  - ≥ 20 MCs / HPF in GI biopsies is proposed as a diagnostic criterion
    - Jakate S, Demeo M, John R, et al. Arch Pathol Lab Med 2006;130(3):362-7. PMID: 16519565
    - Akhavein M A, Patel NR, Muniyappa PK, et al. Gastroenterol Res Pract 2012;2012:950582. PMID: 22577375
  - ***However threshold values may depend on the stain used*** (c-kit IHC more sensitive than tryptase IHC)

When is it useful to report mast cell numbers ? (2)

Mast cell evaluation in gastrointestinal biopsies: should we be counting? A critical review and practical guide for the surgical pathologist

Sameer Shivji, James Ryan Conner & Richard Kirsch
Department of Pathology & Laboratory Medicine, Mount Sinai Hospital, Toronto, ON, Canada

Histopathology 2023, 82, 960–973.

- Various inflammatory conditions (Hp gastritis, bile reflux gastropathy, peptic duodenitis, celiac disease, IBD, microscopic colitis, parasitic infections, eosinophilic gastroenteritis, IBS):
  - ↑ MC numbers when compared with healthy controls
  - However, ***large differences in MC counts between normal GI segments***
  - However, ***no significant differences in MC counts between pts and healthy controls in at least 3 studies***:
    - Hahn HP, Hornick JL. Am J Surg Pathol 2007;31(11):1669-76. PMID: 18059223
    - Doyle LA, Sepehr GJ, Hamilton MJ, et al. Am J Surg Pathol 2014 Jun;38(6):832-43. PMID: 24618605
    - Sethi A, Jain D, Roland BC, et al. Arch Pathol Lab Med 2015;139(2):225-32. PMID: 25611105

EVALUATE GI BIOPSIES FOR MAST CELLS ONLY IN THE CONTEXT OF

POSSIBLE / KNOWN SYSTEMIC MASTOCYTOSIS

- TO RULE OUT THIS DISEASE WHEN THERE IS AN ABNORMAL INFLAMMATORY INFILTRATE ON H&E
- TO CONFIRM GI INVOLVEMENT IN PATIENTS WITH KNOWN SYSTEMIC MASTOCYTOSIS

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EHA EUROPEAN HEMATOLOGY ASSOCIATION

Guideline Article - Consensus based

OPEN ACCESS

Updated Diagnostic Criteria and Classification of Mast Cell Disorders: A Consensus Proposal

Peter Valent[1,2], Cem Akin[3], Karin Hartmann[4,5], Ivan Alvarez-Twose[6], Knut Brockow[7], Olivier Hermine[8], Marek Niedoszytko[9], Juliana Schwaab[10], Jonathan J. Lyons[11], Melody C. Carter[12], Hanneke Oude Elberink[13], Joseph H. Butterfield[14], Tracy I. George[15], Georg Greiner[2,16], Celalettin Ustun[17], Patrizia Bonadonna[18], Karl Sotlar[19], Gunnar Nilsson[20], Mohamad Jawhar[10], Frank Siebenhaar[21], Sigurd Broesby-Olsen[22], Selim Yavuz[23], Roberta Zanotti[24], Magdalena Lange[25], Boguslaw Nedoszytko[25,26], Gregor Hoermann[2,27], Mariana Castells[28], Deepti H. Radia[29], Javier I. Muñoz-Gonzalez[30], Wolfgang R. Sperr[1,2], Massimo Triggiani[31], Hanneke C. Kluin-Nelemans[32], Stephen J. Galli[33], Lawrence B. Schwartz[34], Andreas Reiter[10], Alberto Orfao[30], Jason Gotlib[35], Michel Arock[36], Hans-Peter Horny[19,37], Dean D. Metcalfe[12]

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Systemic mastocytosis
=
a NEOPLASTIC mast cell disorder
diagnosed on the basis of major & minor criteria

Proposed Refined Major and Minor SM Criteria.

Major criterion:	Multifocal dense infiltrates of mast cells (≥15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s)
Minor criteria:	a. ≥25% of all mast cells are atypical cells (type I or type II) on bone marrow smears or are spindle-shaped in mast cell infiltrates detected in sections of bone marrow or other extracutaneous organs[a]
	b. KIT-activating *KIT* point mutation(s) at codon 816 or in other critical regions of *KIT*[b] in bone marrow or another extracutaneous organ
	c. Mast cells in bone marrow, blood, or another extracutaneous organ express one or more of: CD2 and/or CD25 and/or CD30[c]
	d. Baseline serum tryptase concentration >20 ng/mL (in the case of an unrelated myeloid neoplasm, an elevated tryptase does not count as an SM criterion. In the case of a known HαT, the tryptase level should be adjusted[d]
	If at least 1 major and 1 minor or 3 minor criteria are fulfilled → the diagnosis is SM

[a]In tissue sections, an abnormal mast cell morphology counts in both a compact infiltrate and a diffuse (or mixed diffuse + compact) mast cell infiltrate. However, the spindle-shaped form does not count as an SM criterion when mast cells are lining vascular cells, fat cells, nerve cells, or the endosteal-lining cell layer. In the bone marrow smear, an atypical morphology of mast cells does not count as SM criterion when mast cells are located in or adjacent to bone marrow particles. Morphologic criteria of atypical mast cells have been described previously.[6]

[b]Any type of *KIT* mutation counts as minor SM criterion when published solid evidence for its transforming behavior is available. A list of such *KIT* mutations (including variants in *KIT* codons 417, 501–509, 522, 557–560, 642, 654, 799, 816, 820, 822) is provided in Supplemental Digital Content, Table S6, http://links.lww.com/HS/A201 (KIT-activating mutations are labeled in bold).

[c]All 3 markers fulfill this minor SM criterion when expression in mast cells can be confirmed by either flow cytometry or by immunohistochemistry or by both techniques.

[d]Although the optimal way of adjustment may still need to be defined, one way is to divide the basal tryptase level by 1 plus the extra copy numbers of the alpha tryptase gene. Example, when the tryptase level is 30 and 2 extra copies of the alpha tryptase gene are found in a patient with HαT, the HαT-corrected tryptase level is 10 (30/3 = 10) and thus is not a minor SM criterion.

HαT = hereditary alpha-tryptasemia; SM = systemic mastocytosis.

Systemic mastocytosis (1)

Review

Gastrointestinal Manifestations in Systemic Mastocytosis: The Need of a Multidisciplinary Approach

Magda Zanelli [1,*], Marco Pizzi [2], Francesca Sanguedolce [3], Maurizio Zizzo [4,5], Andrea Palicelli [1], Alessandra Soriano [6,7], Alessandra Bisagni [1], Giovanni Martino [8], Cecilia Caprera [8], Marina Moretti [9], Francesco Masia [9], Loredana De Marco [1], Elisabetta Froio [1], Moira Foroni [1], Giuditta Bernardelli [1], Maria Isabel Alvarez de Celis [10], Alessandro Giunta [4], Francesco Merli [10] and Stefano Ascani [8,11]

Cancers 2021, *13*, 3316. https://doi.org/10.3390/cancers13133316

- Several symptoms:
  - Due to organ infiltration by neoplastic mast cells (bone marrow, skin, liver, spleen, lymph nodes, GI tract)
  - Due to mediator release from the neoplastic mast cells

- GI symptoms are common (60-80% of pts) & often severe:
  - Most often due to mediator release
    - Nausea, vomiting, bloating, cramping, diarrhea, peptic ulcers
  - Less commonly due to organ infiltration
    - GI tract : Malabsorption, weight loss, colonic ulcers ~ Crohn's disease
    - Hepatomegaly, splenomegaly, portal hypertension, ascites

Systemic mastocytosis (2)

Review

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- Many systemic mastocytosis pts do not undergo GI endoscopy
- Reasons for endoscopy:
  - Severe GI complaints
  - Attempt to diagnose SM when bone marrow trephine biopsy negative
- Doyle LA, Sepehr GJ, Hamilton MJ, et al. Am J Surg Pathol 2014;38(6):832-43
  - Most commonly involved: ileum (86%), colon (81%), duodenum (67%), stomach (35%)
  - Endoscopic aspect:
    - Normal in 30-40%
    - Non-specific abnormalities (nodularity, loss of folds, erythema, erosions) in 60%
  - Multiple biopsies necessary to increase detection rate

Systemic mastocytosis (3)

Review

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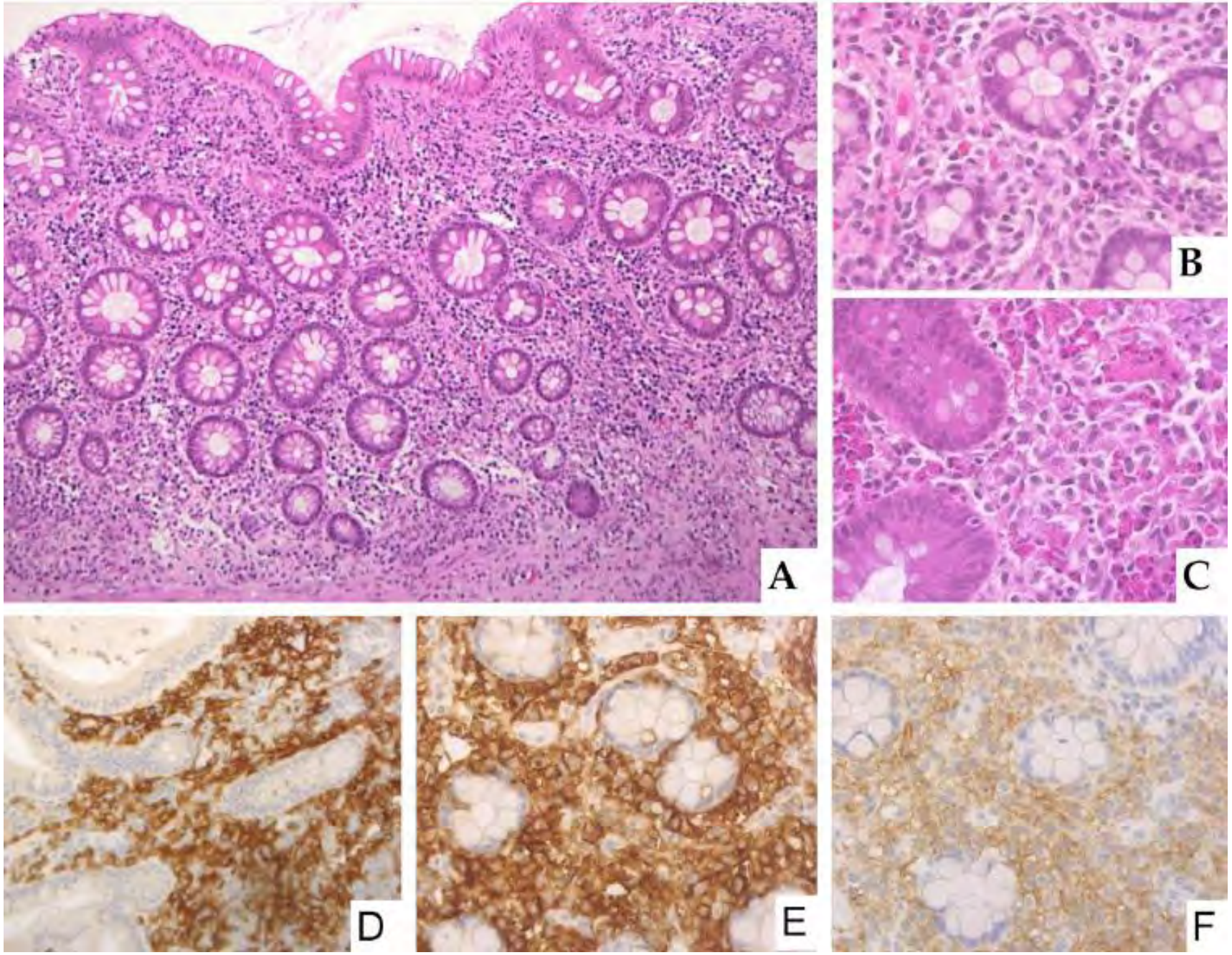
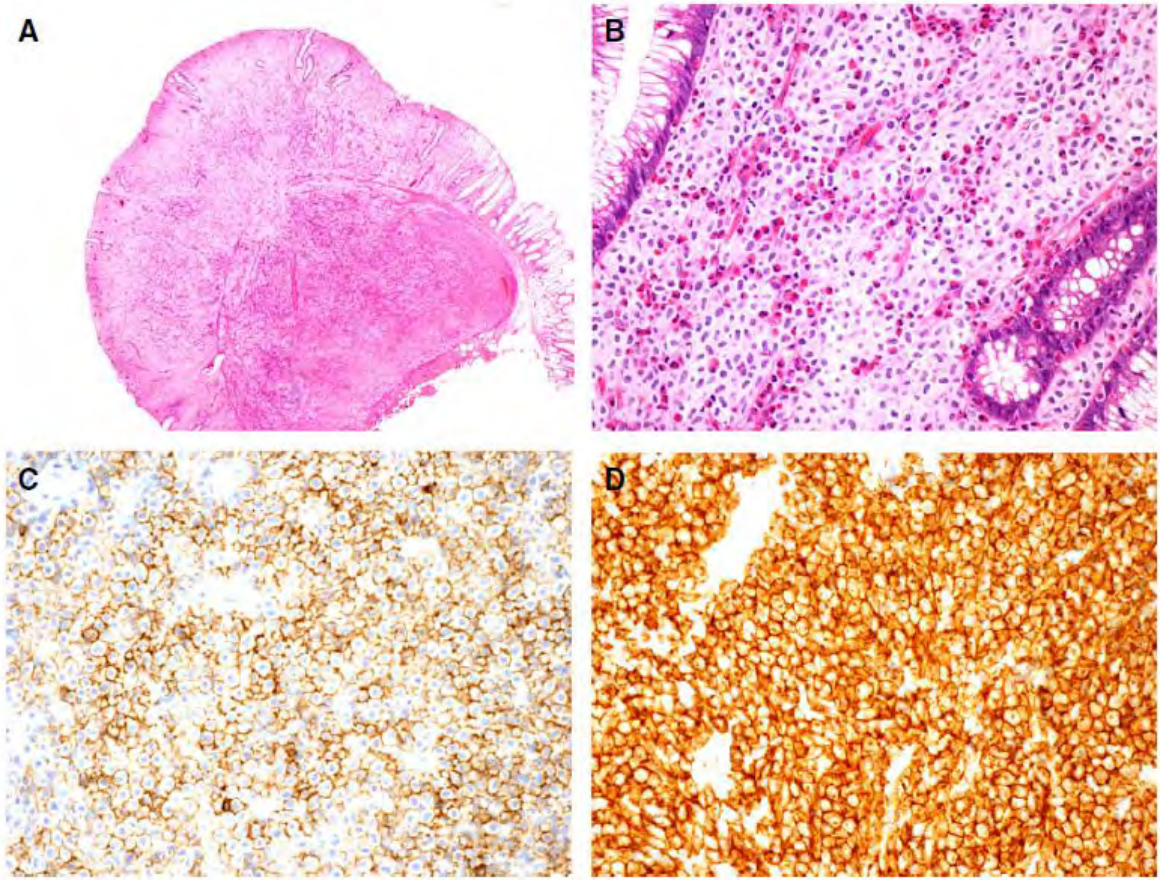
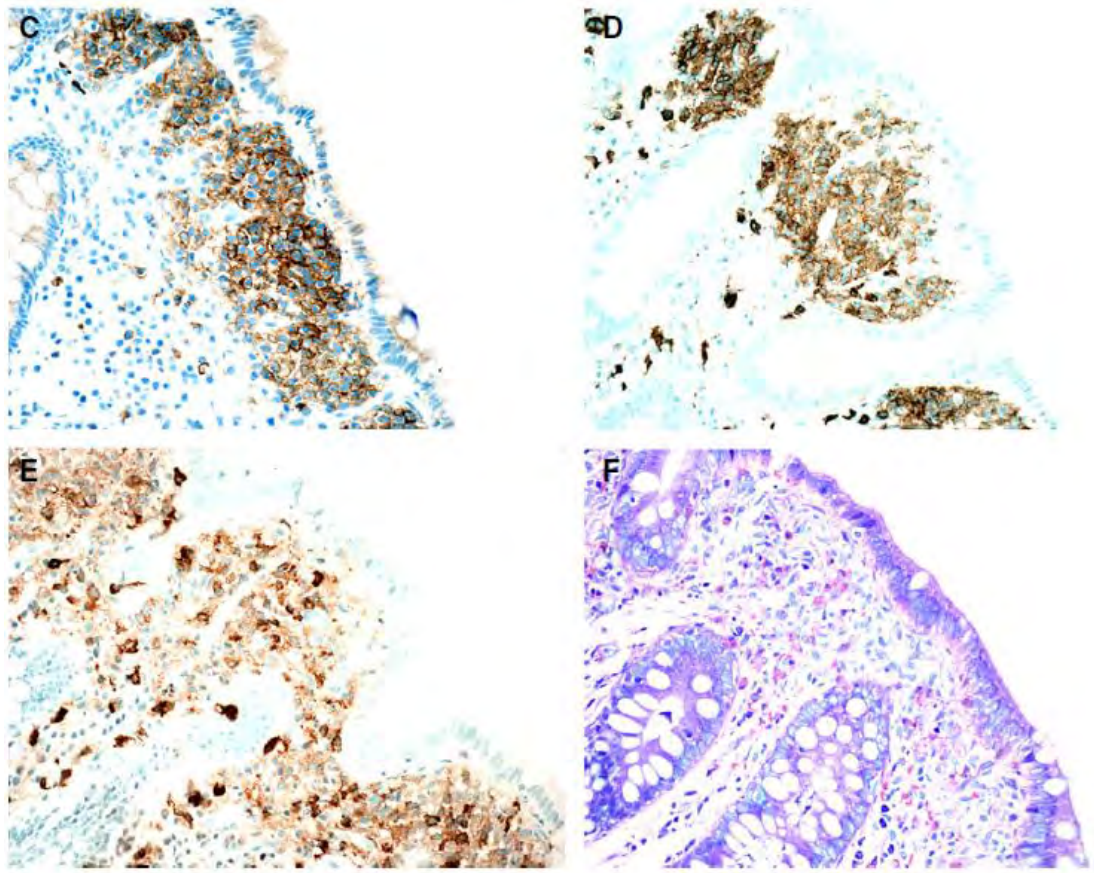
- Look for:
  - **(Tiny) clusters / sheets** of round / ovoid / spindled, pale cells
  - Predominantly in a subepithelial position
  - ! May be admixed with / obscured by huge numbers of eosinophils !
- Perform IHC:
  - For detection of mast cells:
    - **C-kit** = sensitive, but not specific
    - **Tryptase** = more specific, but less sensitive
  - Expression of **CD25** = a hallmark of “mast cell atypia”
    - CD2 is less useful (not always present in neoplastic MCs)
    - CD30 is less useful (not always present in aggressive disease)



(D) Tryptase, (E) c-kit, (F) CD25 (all 400x)



(C) CD25, (D) c-kit



(C) CD25, (D) c-kit, (E) tryptase, (F) Giemsa

Shih AR, Deshpande V, Ferry JA, Zukerberg L. Clinicopathological characteristics of systemic mastocytosis in the intestine. Histopathology 2016;69(6):1021-1027. PMID: 27391777.

MAST CELL DISORDERS OF THE GI TRACT
-
Conclusions, recommendations

- DON'T systematically stain for MCs in (chronic) inflammatory GI diseases / functional disorders
- If you are requested to do this by your clinicians:
  - Comment on the inherent limitations (sampling, biopsy orientation)
  - Make a statement on the uncertainty of this approach (threshholds, overlapping ranges)
  - Mention the relevant pathology literature
  - Stain for c-kit & / tryptase
  - Count in a systematic way
  - Report peak values & means (in 3-5 HPFs) expressed as MC numbers / mm^2
- (determine normal values in your own population ???)
- Our only REALLY IMPORTANT contribution is in the diagnosis of SYSTEMIC MASTOCYTOSIS
  - Take the initiative to stain, even if there is no clinical suspicion

QUESTIONS ?