



How I Handle Mast Cells in GI Biopsies

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Dr. Lam-Himlin declares she has no conflict of interest to disclose.

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Outline

- GIPS Survey Results
- Mast Cell Disorders affecting the GI tract
 - Systemic Mastocytosis
 - Mastocytic Enterocolitis
 - Mast Cell Activation Syndrome
- My (limited) experience
- Open discussion

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Survey Results: A Focus on Mastocytic Enterocolitis

86 respondents

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"We do mast cell counts on all patients with a history of diarrhea and have received many positive comments from our physicians" (1)

How often do you receive requests for mast cell stains?

"Have not had request recently since no proof in literature that disease exists" (1)

Frequency	Percentage
I have never received a request	33%
Rarely (1-5 times per year)	47%
Sometimes (every 1-2 months)	9%
Regularly (at least once a month)	5%
Routinely (at least once a week or more)	5%
Other (please specify) (2)	2%

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When do you initiate an order for mast cell stains to rule out mastocytic enterocolopathy in cases of chronic diarrhea in which the COLONIC biopsies appear normal?

When do you initiate an order for mast cell immunostains to rule out mastocytic enterocolopathy in cases of chronic diarrhea in which the DUODENAL biopsies appear normal by H&E?

Prompted by H&E features (3):

- Unusual infiltrate
- Numerous eosinophils
- Numerous mast cells

"Mastocytic enterocolopathy does not exist. Some patients with similar signs/symptoms have mast cell activation syndrome, whereas occasional patients have systemic mastocytosis involving the GI mucosa. I order mast cell stains to exclude the latter or to teach referring pathologists and clinicians." (1)

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Don't do it (10)

- Never requested
- Not a real disease
- I would never count mast cells - see Am J Surg Pathol. 2014;38(6):832-43

Mast cell immunostains to rule out enterocolopathy, how do you report them?

Count 10 HPF and report average:

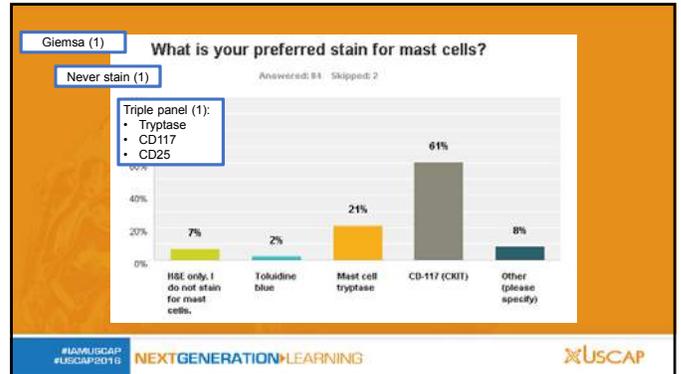
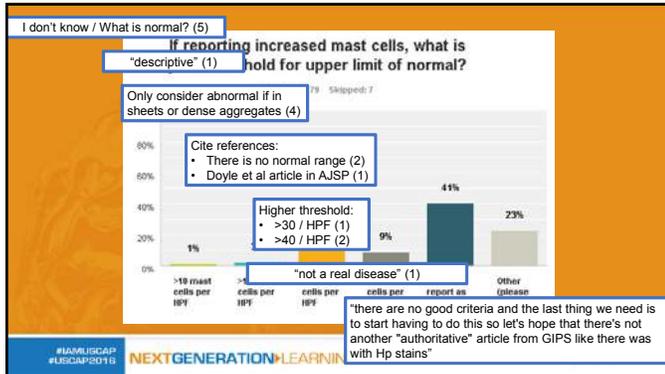
- >20 report as mastocytic enterocolopathy (2)
- Report both peak value and mean value (1)
- Report, but comment the value is meaningless (2)

"I tell the clinician why they are silly"

"the only thing that should be reported is the pathologist that regularly does (and charges for) these stains"

"as the crazy requester wishes"

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Conclusions from survey

- Wide range of practice exists
- No consensus method
- GIPS members have strong opinions on this topic

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Mast cell disorders affecting the GI tract

- Systemic Mastocytosis (SM)
- Mastocytic Enterocolitis (ME)
- Mast Cell Activation Syndrome (MCAS)

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Mastocytosis

Clonal neoplastic proliferation

- Urticaria pigmentosa
- Telangiectasia macularis eruptiva perstans
- Diffuse cutaneous mastocytosis
- Solitary mastocytoma
- Systemic mastocytosis

WHO Diagnostic Criteria

Major criterion	Minor criteria
Multifocal, dense aggregates of mast cells (5 or more) detected in sections of bone marrow (performed) or other extracutaneous organs (eg, gastrointestinal tract, lymph nodes, liver, or spleen), and confirmed by tryptase immunohistochemistry or other special stains.	a. In biopsy section, more than 20% of the mast cells in the tissue have atypical morphology or spindle shapes, or all of the mast cells in an aggregate were more than 20% are immature or atypical.
	b. Mast cells co-express CD117 with CD2 and/or CD25.
	c. Detection of KIT point mutation at codon D115 in bone marrow, blood, or other extracutaneous organs.
	d. Genes from tyrosine phosphorylation >20 ng/ml (not a valid criteria in cases of systemic mastocytosis with associated clonal hematologic non-mast-cell lineage disease).

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Systemic Mastocytosis

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Mastocytic Enterocolitis

New entity proposed by Jakate et al
Arch Pathol Lab Med: Vol 130, March 2006

- Chronic intractable diarrhea (adults)
- >20 mast cells per HPF
- Patients respond to drugs inhibiting mast cell mediators

Conclusions:

- "Increased": >20 mast cells/hpf (>2 SD above control)
- 70% with increased mast cells
- 67% with response to drug therapy

Patient Group	Mast cell concentration Mean ± SD
50 Controls (adenoma screening)	13.2 ± 3.5
47 Patients (chronic intractable diarrhea)	25.7 ± 4.5
63 Other specific diseases (IBD, celiac dz, collagenous & lymphocytic colitis)	12.4 ± 2.3

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Requests for Mast Cell Counts Increased

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Mast cell activation syndrome: A newly recognized disorder with systemic clinical manifestations

Matthew J. Hamilton, MD,* Jason L. Hornick, MD, PhD,* Cem Akin, MD, PhD,* Mariana C. Castells, MD, PhD,* and Norton J. Greenberger, MD* Boston, Mass

J Allergy Clin Immunol. 2011 Jul;128(1):147-152

- Pts have at least 4 signs and symptoms of mast cell degranulation:
 - Abdominal pain
 - Diarrhea
 - Flushing
 - Dermatographism
 - Memory and concentration difficulties
 - Headache
- Laboratory tests showing increased mast cell mediators:
 - Serum tryptase
 - Serum mature tryptase
 - Urine Histamine
 - Serum/plasma PGD₂
- Response to medications targeting mast cell mediators
- Pts do not meet WHO criteria for SM or clonal disorder (MMCAS)

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- Response to medications targeting
- Pts do not meet WHO criteria for SM or clonal disorder (MMCAS)

Site of biopsy	No. of patients	Meaning (range)*	Range (normal)†
Stomach	7	17 (13)	14-28 (6-23)
Duodenum	7	23 (27)	18-26 (4-51)
Left colon	5	20 (21)	15-27 (10-31)
Right colon	4	17 (21)	12-18 (10-31)

*Data from Haber and Hornick.¹⁷

Conclusions:

1. Histology of MCAS is normal
2. No difference in mast cell counts between MCAS and reference standard

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Am J Surg Pathol. 2014 Jun;38(6):832-43. doi: 10.1097/PAS.0000000000000190.

A clinicopathologic study of 24 cases of systemic mastocytosis involving the gastrointestinal tract and assessment of mucosal mast cell density in irritable bowel syndrome and asymptomatic patients.

Coyla LA,¹ Szepietu CJ, Hamilton MJ, Akin C, Castells MC, Hornick JL

Aims of study:

1. Determine utility of GI biopsies in diagnosis of SM
2. Characterize clinical, histologic, and immunohistochemical features of SM in GI tract
3. Determine mast cell density in normal colonic mucosa
4. Compare findings with diarrhea predominant IBS

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A clinicopathologic study of 24 cases of systemic mastocytosis involving the gastrointestinal tract and assessment of mucosal mast cell density in irritable bowel syndrome and asymptomatic patients.

Dovis LA¹, Saxeer GU, Hamilton MJ, Asin C, Castells MC, Hornick JL

Patient Group	Mean mast cell count in 5 contiguous HPF (range)
100 asymptomatic (adenoma screening)	26 (11-55)
100 IBS, diarrhea predominant	30 (13-59)

Conclusions

- Mast cell density in asymptomatic patients is highly variable
- IBS patients slightly higher, but overlap in range with control is too great to be clinically useful

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Arch Pathol Lab Med, 2015 Feb;139(2):225-32. doi: 10.5959/arpa.2013-0594.OA.

Performing colonic mast cell counts in patients with chronic diarrhea of unknown etiology has limited diagnostic use.

Sethi A¹, Jain D, Roland BC, Kinzel J, Gibson J, Schrader R, Hanson JA

Conclusions

- Mast cell counts are uninterpretable on random Bx
- Mast cell counts are increased in the left colon in CDUE
- Wide overlapping range with normal colon results in nondiscriminatory cutoff value

Patient Group	Mean highest mast cell count in 1 HPF (±SD)	Right Colon Mean (±SD)	Left Colon Mean (±SD)
89 asymptomatic (adenoma screening)	24.1 (±8.7)	25.4 (±9.0)	22.2 (±8.6)
76 Chronic diarrhea of unknown etiology (CDUE)	30.7 (±10.5)	28.2 (±11.0)	31.0 (±15.9)

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What do my clinicians think about this?

- Number of requests for "r/o mast cells" has decreased dramatically
- Some allergy/immunology clinicians still request, but recognize the data do not support counting mast cells.
- Neurologists have shown interest
 - Autonomic dysfunction (e.g. postural orthostatic tachycardia syndrome/POTS)
 - Ehlers-Danlos syndrome
- High interest in developing markers for gut mast cell mediators

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What I do

Any of the following histologic features:

- ↑ visible mast cells
- ↑ density eosinophils
- Unexplained lamina propria pallor
- Unclassifiable cells with pale cytoplasm

OR

Request from clinician to "r/o mast cells"

Perform CD117 & CD25 immunostains

CD117+ CD25+

CD117+ CD25-

"Up front" CD117

Systemic Mastocytosis
NOTE: Biopsies show confluent sheets of CD117+ mast cells with atypical spindled morphology and aberrant co-expression of CD25. The presence of abnormal mast cell clusters in an extracutaneous site fulfills diagnostic criteria for systemic mastocytosis (World Health Organization: one major and one minor criterion.)

Single Scattered Mast Cells
NOTE: CD117 immunostain highlights single scattered mast cells without confluence and without aberrant co-expression of CD25. These findings provide no evidence of systemic mastocytosis.

Single Scattered Mast Cells
NOTE: At the request of the clinician, CD117 immunostain highlights # mast cells per high powered field. The cells are single and scattered, without confluence.

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Discussion

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	Jakate et al 2006	Hamilton et al 2011	Doyle et al 2014	Sethi et al 2015
Patient group	Chronic intractable diarrhea (AGA w/u)	Evidence of mast cell degranulation (symptoms/labs)	Diarrhea predominant IBS (clinical dx)	Chronic diarrhea of unknown etiology (AGA w/u and nl bx)
Mast cell stain				
Counting method				
Conclusion				

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Mast cell stain	Mast Cell Tryptase and Toluidine Blue <ul style="list-style-type: none"> Found that Toluidine Blue highlighted 30-60% fewer mast cells 	Mast Cell Tryptase and CD117	CD117 <ul style="list-style-type: none"> Found that tryptase was negative in a subset of neoplastic mast cells 	CD117
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Counting method	Average of 10 HPFs across at least 2 tissue fragments	Average of 10 contiguous HPF's (Hain and Hornick 2007)	Average in 5 contiguous HPF's in highest density area	Single HPF in highest density area
Conclusion				

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Counting method	Average of 10 HPFs across at least 2 tissue fragments	Average of 10 contiguous HPF's (Hahn and Hornick 2007)	Average in 5 contiguous HPF's in highest density area	Single HPF in highest density area
Conclusion	67% of these patients who also have >20 mast cells/HPF will show symptomatic improvement with treatment	Patients with MCAS benefit from treatment, but not a histologic diagnosis	IBS patients have slightly higher mast cell counts, but the overlap with normal range is too great to be clinically useful	Mast cell counts slightly higher than compared to normal, but no discriminatory cutoff value exists

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What do you think?

- **Patient selection:** Could a subset of patients from Jakate's study (ME) fulfill criteria for MCAS?
- **Stain choice:** Could Mast Cell Tryptase differentiate normal mast cells from abnormal mast cells better than CD117, thereby explaining the wider differences between normal and abnormal in Jakate's study?
- Is there a role for mast cell staining in any subset of patients?
- Does clarification require additional study? (suggest design?)

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