How I Handle Mast Cells in GI Biopsies

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

• GIPS Survey Results

• Mast Cell Disorders affecting the GI tract
  • Systemic Mastocytosis
  • Mastocytic Enterocolitis
  • Mast Cell Activation Syndrome

• My (limited) experience

• Open discussion
Survey Results: A Focus on Mastocytic Enterocolitis

86 respondents
How frequently do you receive requests for mast cell counts?

Answered: 86   Skipped: 0

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

- Never: 50%
- Routinely: 1%
- Only upon clinician request: 12%
- For certain clinicians who always want them: 6%
- Other (please specify) (5)

Answered: 86  Skipped: 0

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?

- Never: 50%
- Routinely: 37%
- Only upon clinician request: 5%
- For certain clinicians who always want them: 0%
- Other (please specify) (4)

Answered: 86  Skipped: 0
If you do mast cell immunostains to rule out mastocytic enterocolopathy, how do you report them?

Answered: 74   Skipped: 12

- Peak value of mast cells in one HPF: 35%
- Range of mast cells per HPF: 24%
- "Increased" or "normal": 18%
- Other (please specify): 23%

(HPF: high-power field)
If reporting increased mast cells, what is your threshold for upper limit of normal?

Answered: 79  Skipped: 7

- 1% >10 mast cells per HPF
- 3% >15 mast cells per HPF
- 24% >20 mast cells per HPF
- 9% >25 mast cells per HPF
- 41% I do not report as increased mast cells.
- 23% Other (please specify) (18)
What is your preferred stain for mast cells?

Answered: 84  Skipped: 2

- H&E only. I do not stain for mast cells: 7%
- Toluidine blue: 2%
- Mast cell tryptase: 21%
- CD-117 (CKIT): 61%
- Other (please specify): 8%
Conclusions from survey

• Wide range of practice exists
• No consensus method
• GIPS members have strong opinions on this topic
Mast cell disorders affecting the GI tract

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

Clonal neoplastic proliferation
• Urticaria pigmentosa
• Telangiectasia macularis eruptiva perstans
• Diffuse cutaneous mastocytosis
• Solitary mastocytoma
• Systemic mastocytosis

WHO Diagnostic Criteria

<table>
<thead>
<tr>
<th>Major criterion</th>
<th>Minor criteria</th>
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<tr>
<td>Multifocal, dense aggregates of mast cells (15 or more) detected in sections of bone marrow (preferred) or other extracutaneous organs (eg, gastrointestinal tract, lymph nodes, liver, or spleen), and confirmed by tryptase immunohistochemistry or other special stains</td>
<td>a. In biopsy section, more than 25% of the mast cells in the infiltrate have atypical morphology or spindle shapes; or, of all the mast cells in an aspirate smear, more than 25% are immature or atypical</td>
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<td>b. Mast cells co-express CD117 with CD2 and/or CD25</td>
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<td>c. Detection of KIT point mutation at codon 816 in bone marrow, blood, or other extracutaneous organs</td>
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<td>d. Serum total tryptase persistently &gt;20 ng/ml (not a valid criteria in cases of systemic mastocytosis with associated clonal hematologic non-mast-cell lineage disease)</td>
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Systemic Mastocytosis
Systemic Mastocytosis

H&E

TRYPTASE

CD117

CD25
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

<table>
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<tr>
<th>Patient Group</th>
<th>Mast cell concentration Mean ± SD</th>
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<tr>
<td>50 Controls</td>
<td>13.2 ± 3.5</td>
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<tr>
<td>(adenoma screening)</td>
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<tr>
<td>47 Patients</td>
<td>25.7 ± 4.5</td>
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<tr>
<td>(chronic intractable diarrhea)</td>
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<tr>
<td>63 Other specific diseases</td>
<td>12.4 ± 2.3</td>
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<td>(IBD, celiac dz, collagenous &amp; lymphocytic colitis)</td>
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Requests for Mast Cell Counts Increased
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

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

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

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

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

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<th>Patient Group</th>
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<th>Right Colon Mean (±SD)</th>
<th>Left Colon Mean (±SD)</th>
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<td>89 asymptomatic (adenoma screening)</td>
<td>24.1 (±8.7)</td>
<td>25.4 (±9.0)</td>
<td>22.2 (±8.6)</td>
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<tr>
<td>76 Chronic diarrhea of unknown etiology (CDUE)</td>
<td>30.7 (±10.5)</td>
<td>28.2 (±11.0)</td>
<td>31.0 (±15.9)</td>
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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
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.
Discussion
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Mast cell stain

Counting method

Conclusion
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<td>67% of these patients who also have &gt;20 mast cells/HPF will show symptomatic improvement with treatment</td>
<td>Patients with MCAS benefit from treatment, but not a histologic diagnosis</td>
<td>IBS patients have slightly higher mast cell counts, but the overlap with normal range is too great to be clinically useful</td>
<td>Mast cell counts slightly higher than compared to normal, but no discriminatory cutoff value exists</td>
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THANK YOU