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

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

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

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)

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

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 clinicians why they are silly” (1)

“The only thing that should be reported is the pathologist that regularly does (and charges for) these stains” (1)
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

Mastocytic Enterocolitis

• New entity proposed by Jakate et al
  Arch Pathol Lab Med: Vol 130, Mar 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
67 Patients (chronic intractable diarrhea) | 25.7 ± 4.6
83 Other specific diseases (IBD, celiac dz, collagenous & lymphocytic colitis) | 12.4 ± 2.3
Requests for Mast Cell Counts Increased

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

Matthew J. Harrington, MD, Laura L. Horvath, MD, PhD, PhD, C. Ceza-Aldko, MB, MD, PhD, MD, PhD, C. Cusicka, MD, PhD, and Notoro J. Griesinger, MD, PhD

- 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)

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.

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Mean mast cell count in 5 contiguous HPF (range)</th>
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<tbody>
<tr>
<td>100 asymptomatic (adenoma screening)</td>
<td>26 (11-55)</td>
</tr>
<tr>
<td>100 IBS, diarrhea predominant</td>
<td>30 (13-56)</td>
</tr>
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</table>

### 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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<tr>
<th>Patient Group</th>
<th>Mean highest mast cell count in 1 HPF (±SD)</th>
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<tr>
<td>Right Colon</td>
<td></td>
</tr>
<tr>
<td>Mean (±SD)</td>
<td></td>
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<tr>
<td>89 asymptomatic (adenoma screening)</td>
<td>24.1 (±8.7)</td>
</tr>
<tr>
<td>76 Chronic diarrhea of unknown etiology</td>
<td>30.7 (±10.5)</td>
</tr>
<tr>
<td>Left Colon</td>
<td></td>
</tr>
<tr>
<td>Mean (±SD)</td>
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<td>25.4 (±9.0)</td>
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<tr>
<td>31.0 (±15.0)</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.

### What I do
- Request from clinician to "r/o mast cells".
  - CD117+ CD25+ Systems
    - 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).
  - CD117+ CD25-
    - Single scattered mast cells
      - 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
    - At the request of the clinician, CD117 immunostain highlights single scattered mast cells without confluence and without aberrant co-expression of CD25. These findings provide no evidence of systemic mastocytosis.
Discussion

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Counting method:
Average of 10 HPFs across at least 2 tissue fragments
Average of 10 contiguous HPFs in highest density area
Average in 5 contiguous HPFs in highest density area
Single HPF in highest density area

Conclusion
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<td>Chronic intractable diarrhea (AGA w/u)</td>
<td>Mast Cell Tryptase and Toluidine Blue - Found that Toluidine Blue highlighted 30-60% fewer mast cells</td>
<td>Mast Cell Tryptase and CD117 - Found that tryptase was negative in a subset of neoplastic mast cells</td>
<td>Mast Cell Tryptase and CD117</td>
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**Counting methods**
- 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 normal, but no discriminatory cutoff value exists

**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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