

WHY MAST IT BE SO HARD? MAST CELL DISORDERS OF THE GI TRACT

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The Many Faces of Mastocytosis

MAST CELL ACTIVATION DISEASE(MCAD)

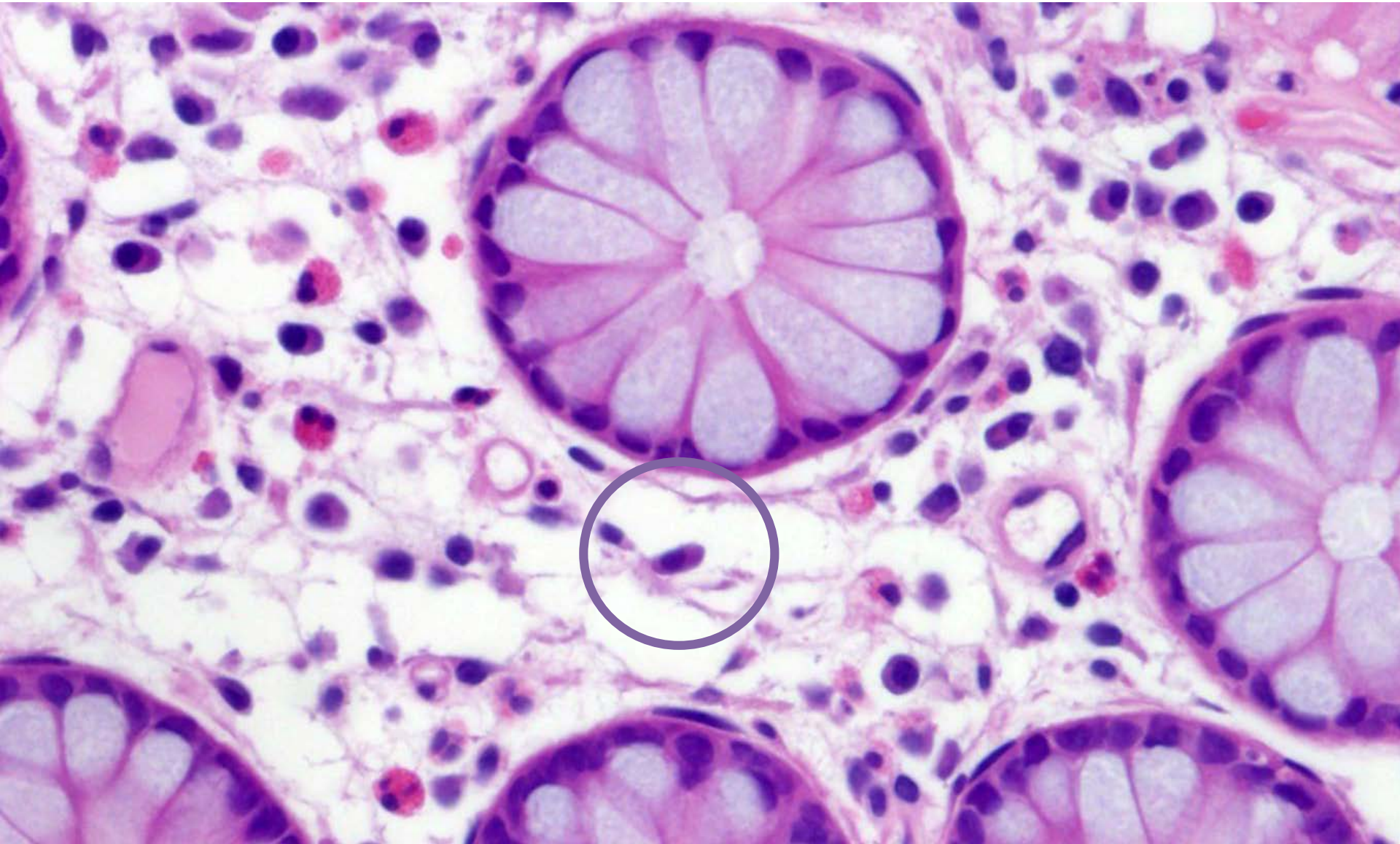
- Cutaneous mastocytosis
- Systemic mastocytosis
- Mast Cell Activation Syndrome- primary, secondary or idiopathic
- Mast cell Leukemia
- Indolent systemic mastocytosis
- Aggressive systemic mastocytosis
- Systemic mastocytosis with an associated clonal hematologic lineage and non-mast cell lineage disease (MDS, AML, lymphoma, others)
- Mastocytic Enterocolitis ??
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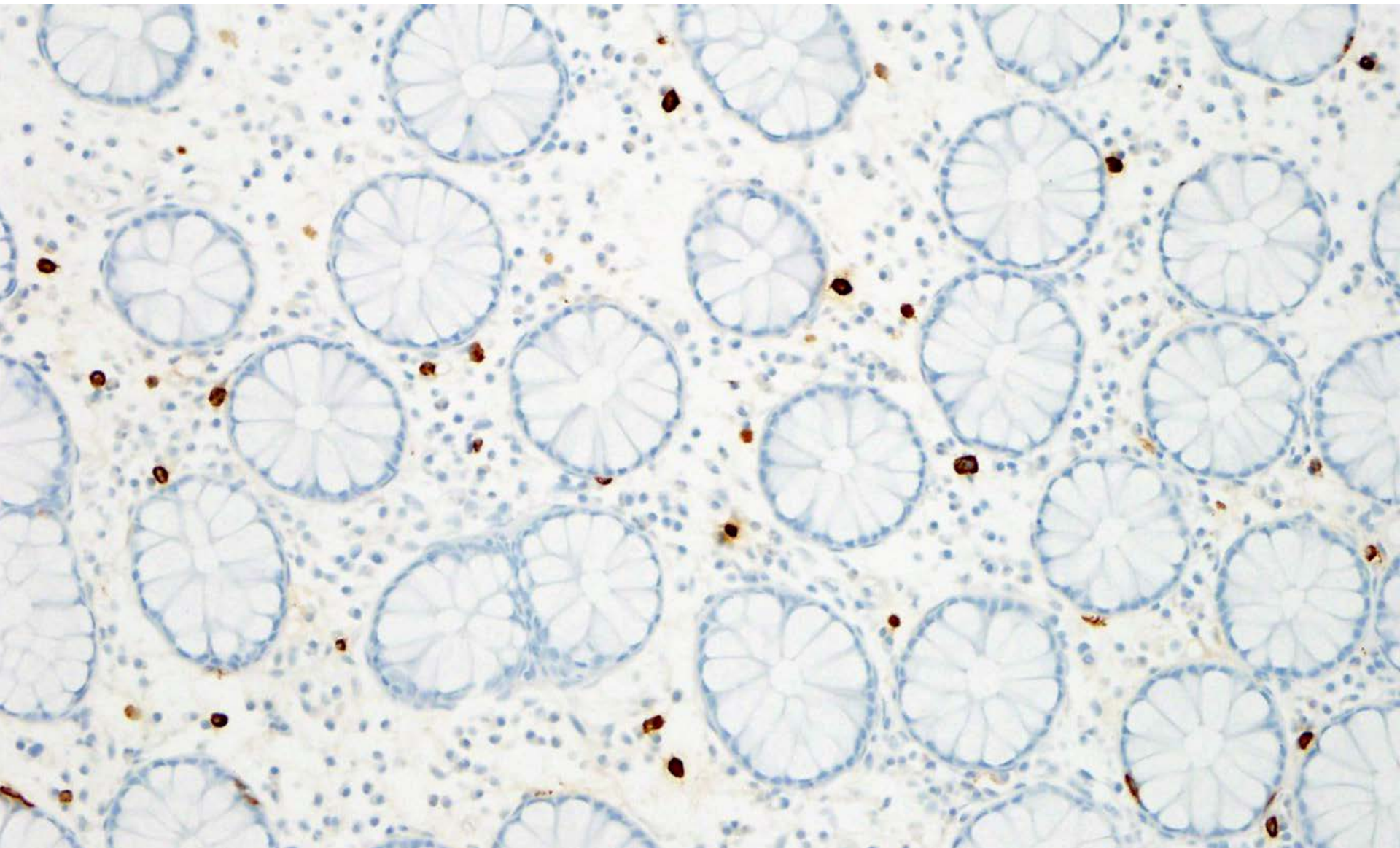
Mastocytosis

Is a heterogeneous disease characterized by mast cell accumulation in one or more organs

Mast Cells- what are they and why are they important

- Important immunoregulatory function
- Found throughout normal tissue
- Number of mast cells at a given site can vary
- Comprise 2-5% of mononuclear cells in the lamina propria of the normal GI tract, representing an average of 13 cells/hpf in the duodenum and colon
- Play an important role in the regulation of gastrointestinal visceral sensitivity and vascular permeability
- Due to the GI tract's large interface, overproduction or over activation of mast cells can lead to GI disorders
- Can be affected by both acute and chronic stress
- Involved in hypersensitivity reactions (particularly "Type I")

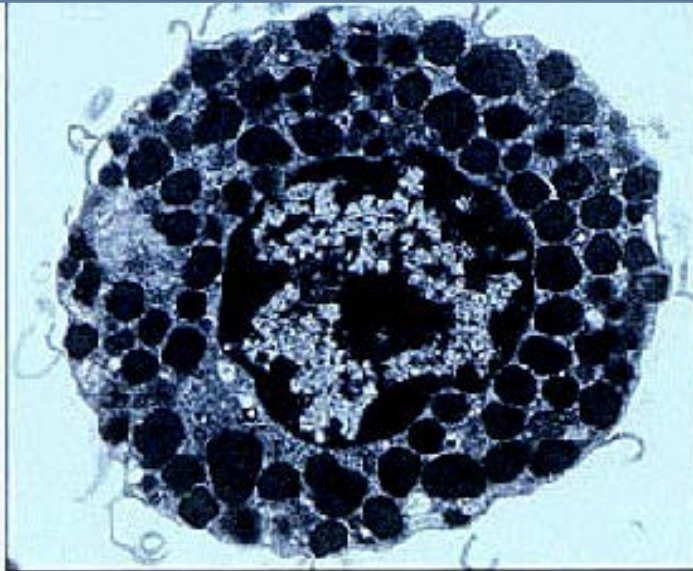




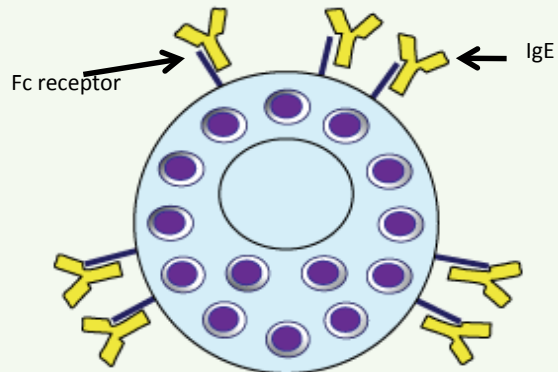
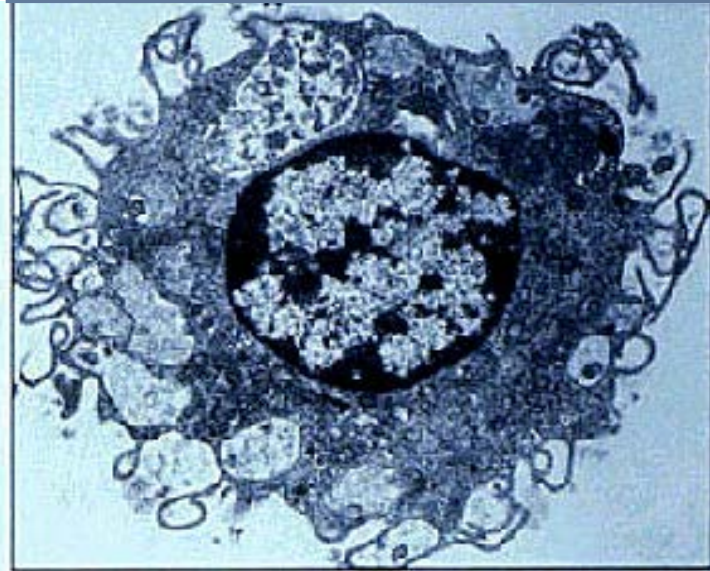
Mast Cell Activation

Once a genetically susceptible individual is sensitized to a given allergen and an IgE Ab forms, subsequent exposure induces manifestations of atopic disease

Resting Mast Cell

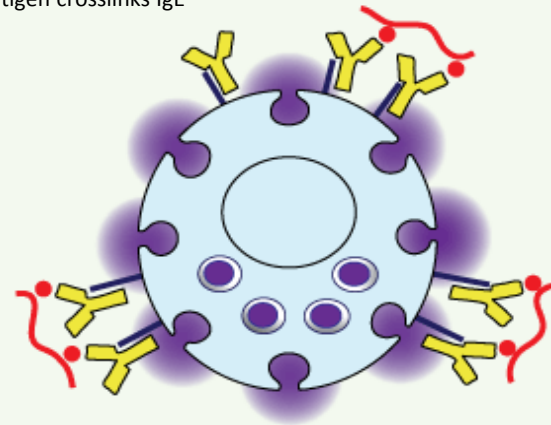


Activated Mast Cell



Granules contain histamine and serotonin

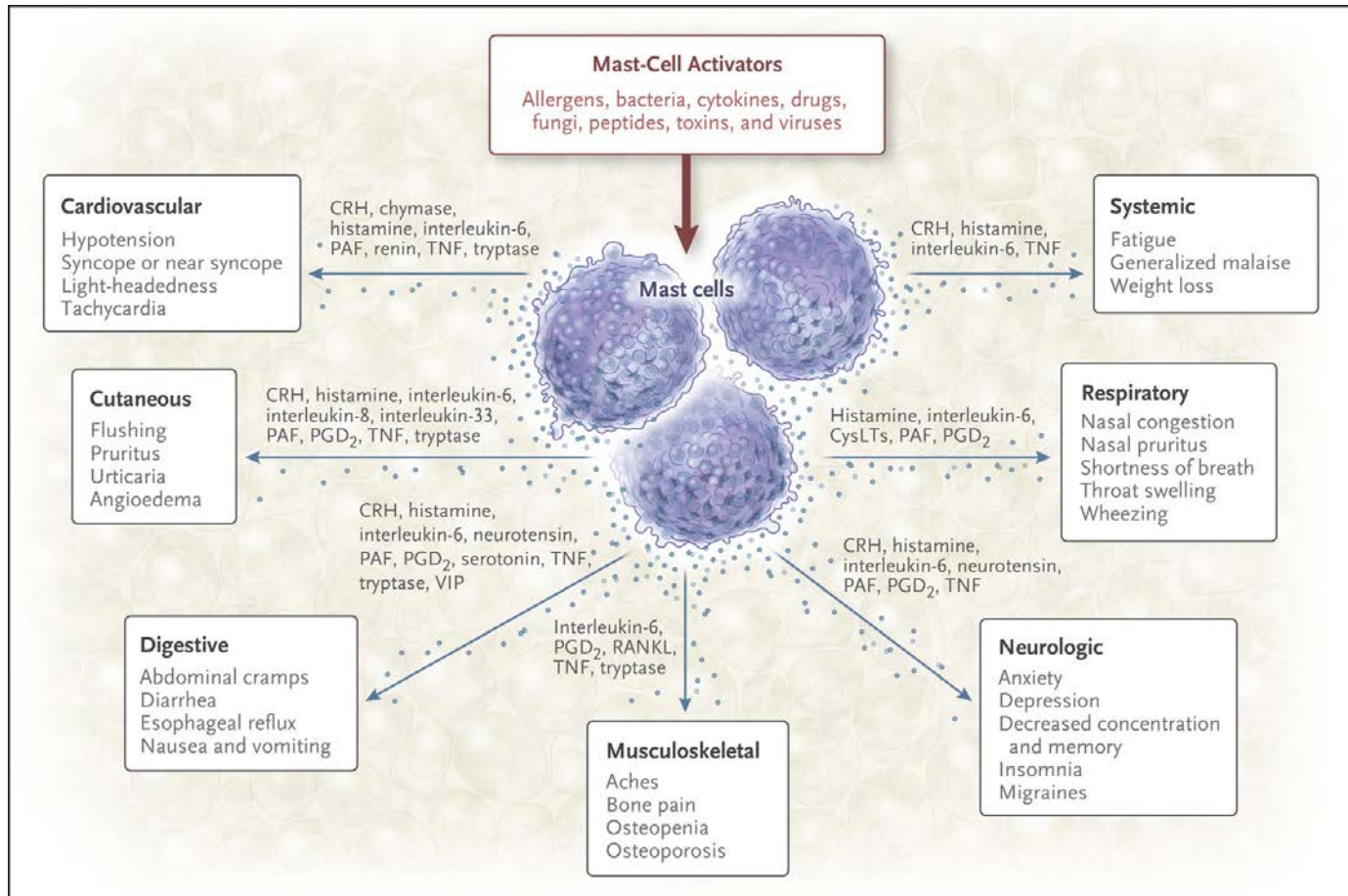
Antigen crosslinks IgE



Release of granule contents

Mast Cell Activators

Akin et al. NEJM 2015; 373:163-172



Potential Mast Cell Triggers

Heat, cold or sudden temperature changes

Stress: emotional, physical, including pain, or environmental (i.e., weather changes, pollution, pollen, pet dander, etc.)

Exercise

Fatigue

Food or beverages, including alcohol

Drugs (opioids, NSAIDs, antibiotics and some local anesthetics) and contrast dyes

Natural odors, chemical odors, perfumes and scents

Venoms (bee, wasp, mixed vespids, spiders, fire ants, jelly fish, snakes, biting insects, such as flies, mosquitos and fleas, etc.)

Infections (viral, bacterial or fungal)

Mechanical irritation, friction, vibration

Sun/sunlight



From a clinical perspective..... Or how the picture becomes even less clear

Any patient with a mast cell disorder can potentially react to any trigger, and triggers can change over the course of the disease.

In addition....patients may experience reactions to virtually any mediator, including medications that they have tolerated previously.

And even less clear, because.....

Conditions That Can Mimic Mast Cell Disorders

Table 1. Conditions That Can Mimic Mast-Cell Disorders.

Cardiac conditions

Coronary hypersensitivity (the Kounis syndrome)*
Postural orthostatic tachycardia syndrome

Endocrine conditions

Fibromyalgia
Parathyroid tumor
Pheochromocytoma
Carcinoid syndrome

Digestive conditions

Adverse reaction to food*
Eosinophilic esophagitis*
Eosinophilic gastroenteritis*
Gastroesophageal reflux disease
Gluten enteropathy
Irritable bowel syndrome
Vasoactive intestinal peptide–secreting tumor

Immunologic conditions

Autoinflammatory disorders such as deficiency of interleukin-1–receptor antagonist*
Familial hyper-IgE syndrome
Vasculitis*

Neurologic and psychiatric conditions

Anxiety
Chronic fatigue syndrome
Depression
Headaches
Mixed organic brain syndrome
Somatization disorder
Autonomic dysfunction
Multiple sclerosis

Skin conditions

Angioedema*
Atopic dermatitis*
Chronic urticaria*
Scleroderma*

* Localized mast-cell activation can occur.

Case

50 y/o female

10/13 noted sharp LLQ pain with h/o intermittent itching across her body that occurs several times a week. Denies rash or hives. Denies diarrhea. History of constipation

8/16 Colonoscopy: Indication- generalized abdominal pain and constipation. TI and colonic mucosa normal. Biopsies from the right colon showed confluent infiltrate of CD117 positive mast cells which also co-expressed CD25

8/16 EGD: Indication- epigastric pain, constipation/diarrhea, h/o gluten intolerance. Erosive gastritis was found. Biopsies from stomach were normal. Those from duodenum showed surface lymphocytosis with normal villous architecture

9/16 Bone marrow biopsy performed elsewhere and reviewed at MM showed myeloproliferative disorder with abnormal megakaryocytes

9/16 CBC showed increased platelets and she was diagnosed with essential thrombocytosis. CALR mutation was positive

10/16 repeat bone marrow biopsy at MM showed scattered mast cells. Some were CD25+

Case, cont.

10/16 Further w/u: Kit D816V was negative in peripheral blood.

24 hour urine showed increase in methyl histamine
LTE 4 was normal
Tryptase was 5.2 ng/ml

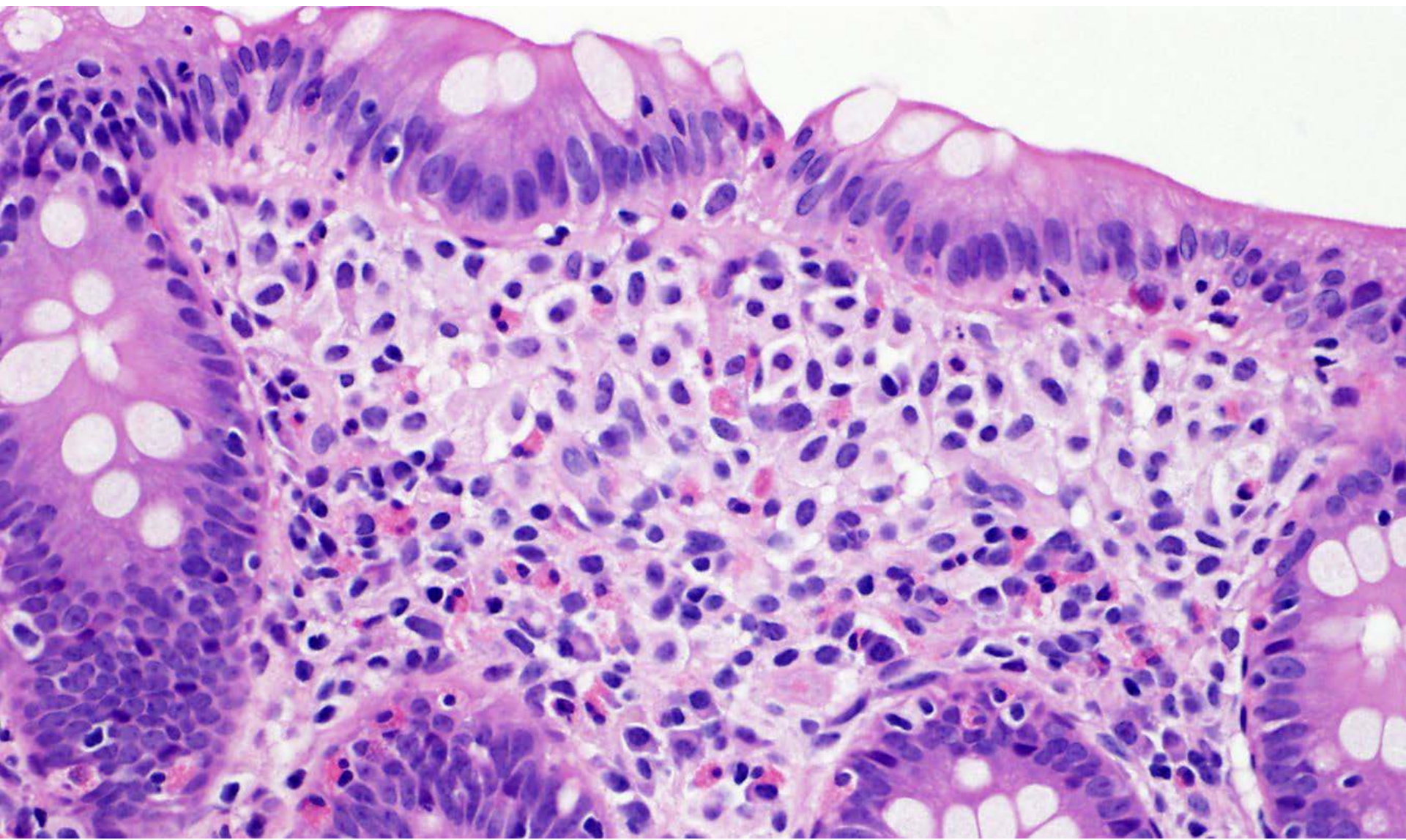
PMH: IBS-C; asthma-like symptoms; allergic rhinitis; gluten sensitivity; anxiety; essential thrombocytosis, tachycardia

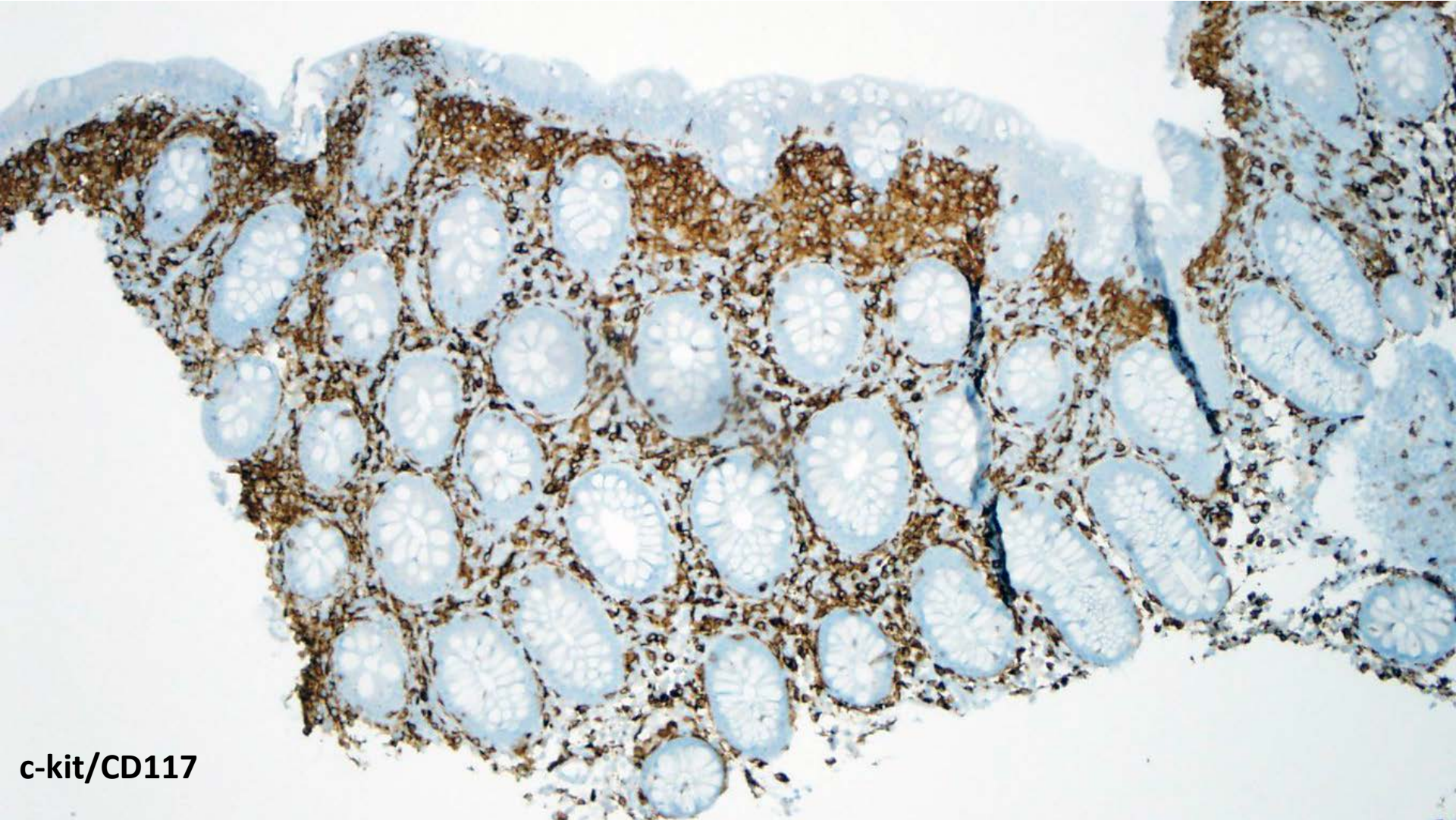
PSH: Breast surgery; hemorrhoidectomy

Medications: Allegra 180 mg qd; Zyrtec q PM; Prilosec 20 mg daily

PE: Unremarkable. No urticaria or angioedema. Not tachycardic

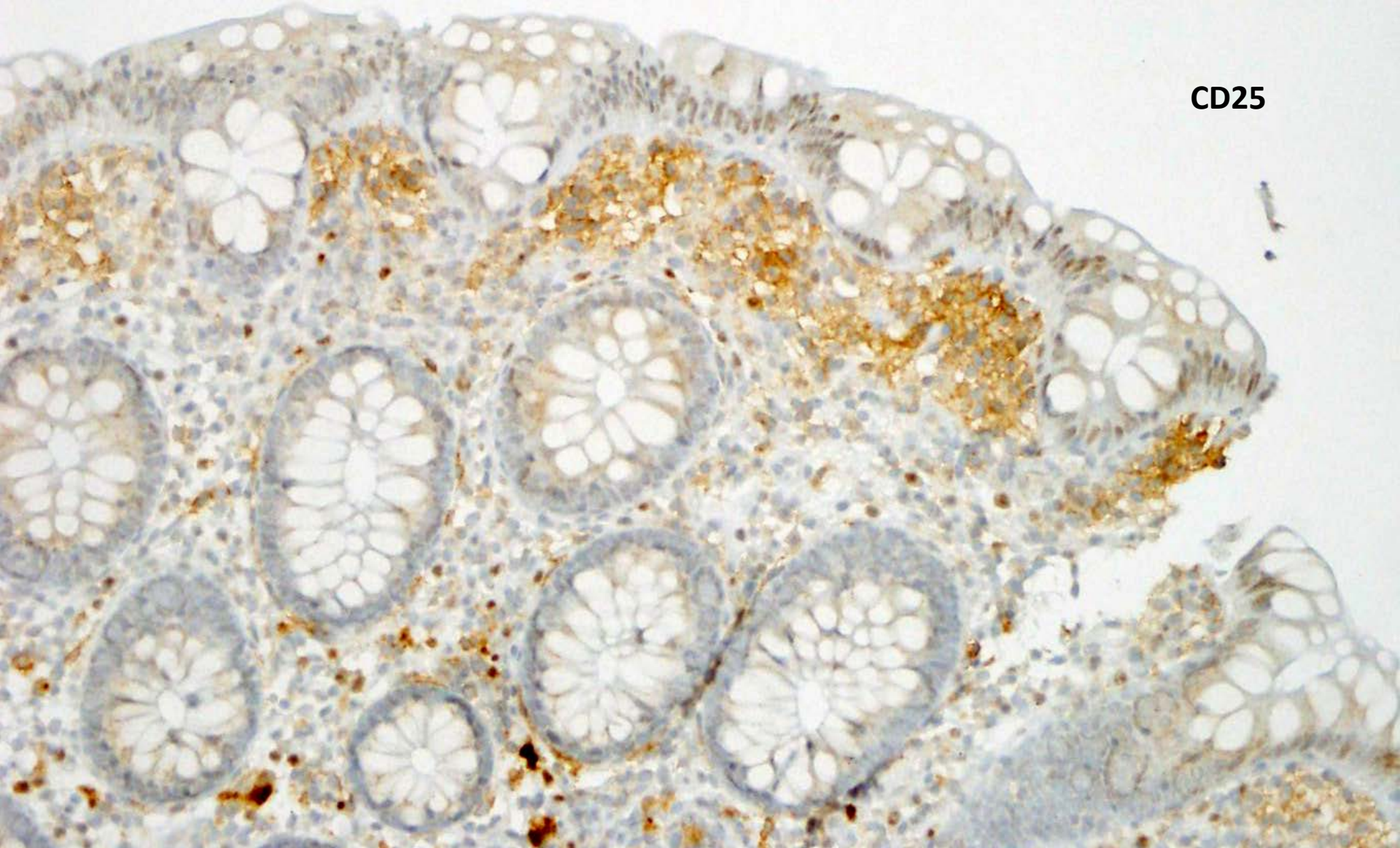






c-kit/CD117

CD25



Systemic Mastocytosis

- Clonal proliferation of mast cells in various extracutaneous organs
 - About 80% of mastocytosis patients have skin involvement
- Most commonly involved sites: liver, spleen, bone marrow and GI tract
- Most cases associated with a *KIT* mutation
- Up to 93% involve codon 816 (*KIT* D816V)
- Symptoms result from the infiltrated organ and mast cell mediator release
- Infiltration can result in organ dysfunction in aggressive cases
- GI symptoms present in 60-80% of cases
 - Abdominal pain and diarrhea
 - Esophagitis, PUD and intestinal malabsorption
- Signs
 - Darier's sign (wheal/flare reaction on stimulation of skin with mast cell infiltrates)
 - Organomegaly (spleen, liver, adenopathy)
 - GI findings: nodules, pigment, thickened folds
 - Variety of hematological findings

Diagnostic Criteria For Cutaneous and Systemic Mastocytosis

Cutaneous mastocytosis (CM)

Skin lesions demonstrating the typical clinical findings of urticaria pigmentosa/maculopapular cutaneous mastocytosis, diffuse cutaneous mastocytosis or solitary mastocytoma, and typical histologic infiltrates of mast cells in a multifocal or diffuse pattern in an adequate skin biopsy. In addition, a diagnostic prerequisite for the diagnosis of CM is the absence of features/criteria sufficient to establish the diagnosis of SM.



Systemic mastocytosis (SM)

The diagnosis of SM can be made when the major criterion and one minor criterion or at least three minor criteria are present.

Major criterion:

Multifocal, dense infiltrates of mast cells (≥ 15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s).

Minor criteria:

1. In biopsy sections of bone marrow or other extracutaneous organs, $>25\%$ of the mast cells in the infiltrate are spindle-shaped or have atypical morphology or, of all mast cells in bone marrow aspirate smears, $>25\%$ are immature or atypical.
2. Detection of an activating point mutation at codon 816 of *KIT* in bone marrow, blood, or another extracutaneous organ.
3. Mast cells in bone marrow, blood, or other extracutaneous organs express CD2 and/or CD25 in addition to normal mast cell markers.
4. Serum total tryptase persistently exceeds 20 ng/mL (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid).

Tryptase

- Tryptase is produced by mast cells in a pre-pro form, and stored in granules in the active form. Its release can be measured as a surrogate marker of mast cell burden or activation.
- Median total tryptase levels in the general population are approximately 4.5 to 5ng/ml. Most laboratories have a cutoff value of 10 to 12ng/ml as the upper limit of normal, representing two standard deviations over the mean values of general population.
- Baseline tryptase levels greater than 20ng/ml are suggestive of clonal mast cell disease.

Gastrointestinal Manifestations In Mastocytosis

- These symptoms are more frequent and severe in patients with mastocytosis compared to healthy subjects:
 - Bloating 33% vs 7%
 - Abdominal pain 27% vs 5%
 - Nausea 23% vs 8%
 - Diarrhea 34% vs 1%

Clinical symptoms did not correspond to histologic findings

J Allergy Clin Immunol 2013; 132:866-73

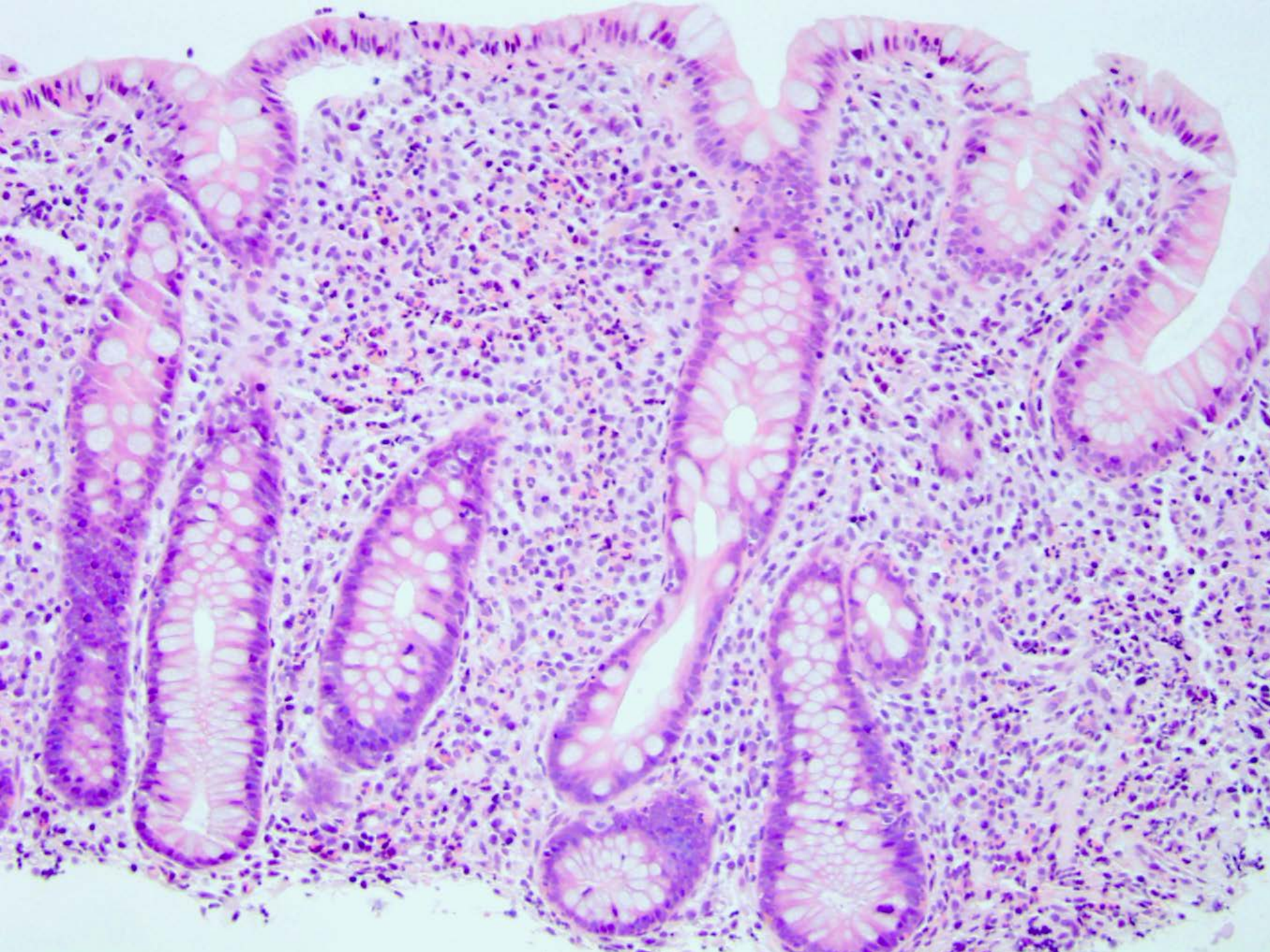
Management of Systemic Mastocytosis

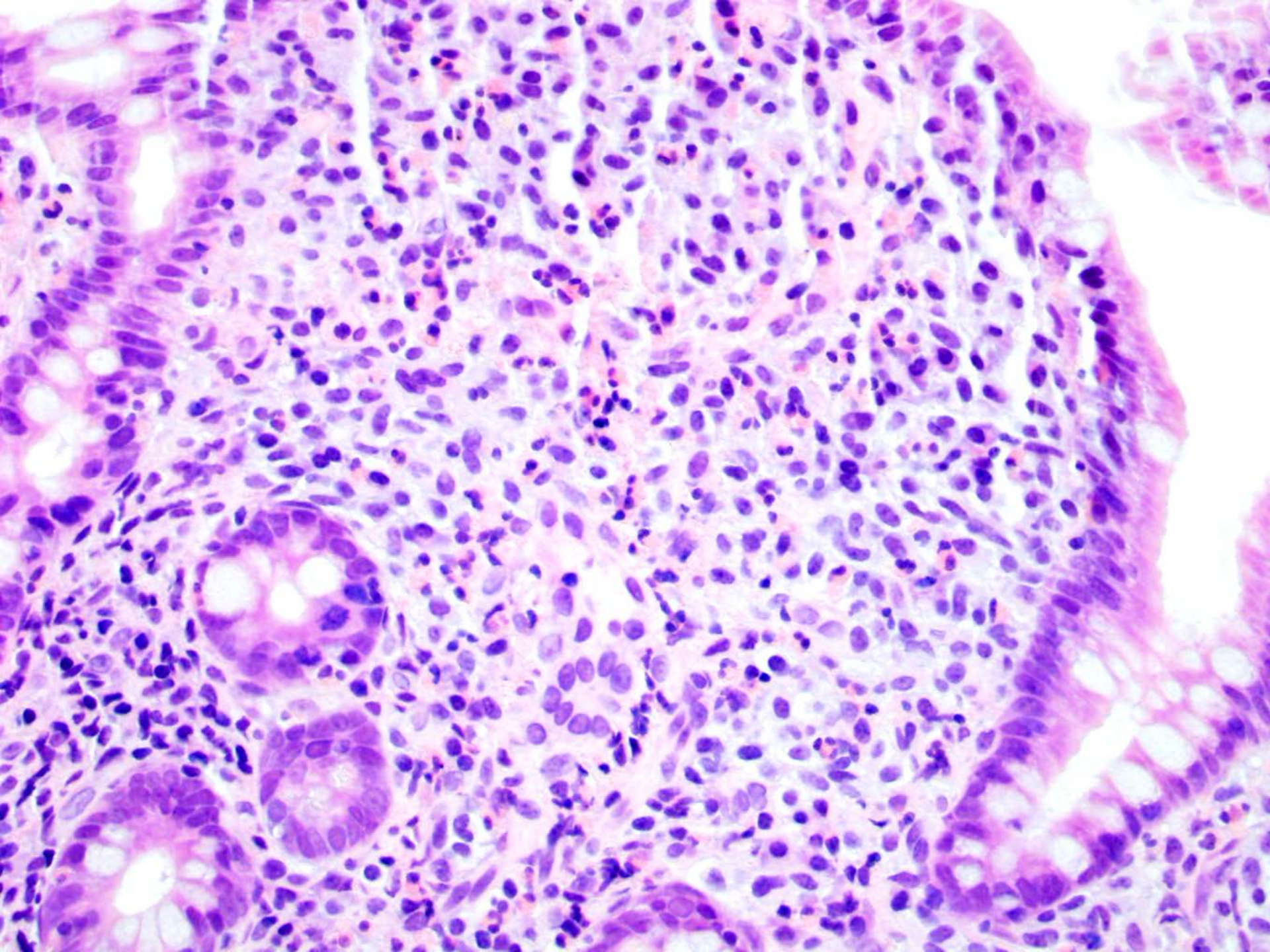
Treatments aimed at stabilizing mast cells and controlling mediator release

- Antihistamines- H1 antihistamines can control flushing and pruritus. H2 antihistamines targeted to decrease hypersecretion of gastric acid and treat symptoms of diarrhea and abdominal cramping
 - Ranitidine 150 mg BID, Pepcid 10 mg BID
- Cromolyn- an inhibitor of mast cell degradation. May improve GI symptoms
- Antileukotriene drugs- Montelukast can improve pruritus and flushing
- Budesonide- alternative treatment if above treatments fail
- Exclusion Diet- Role is unclear
- Fludarabine and interferon- prevent mast-cell infiltration for aggressive disease
- Tyrosine kinase inhibitors- to target the *KIT* mutation

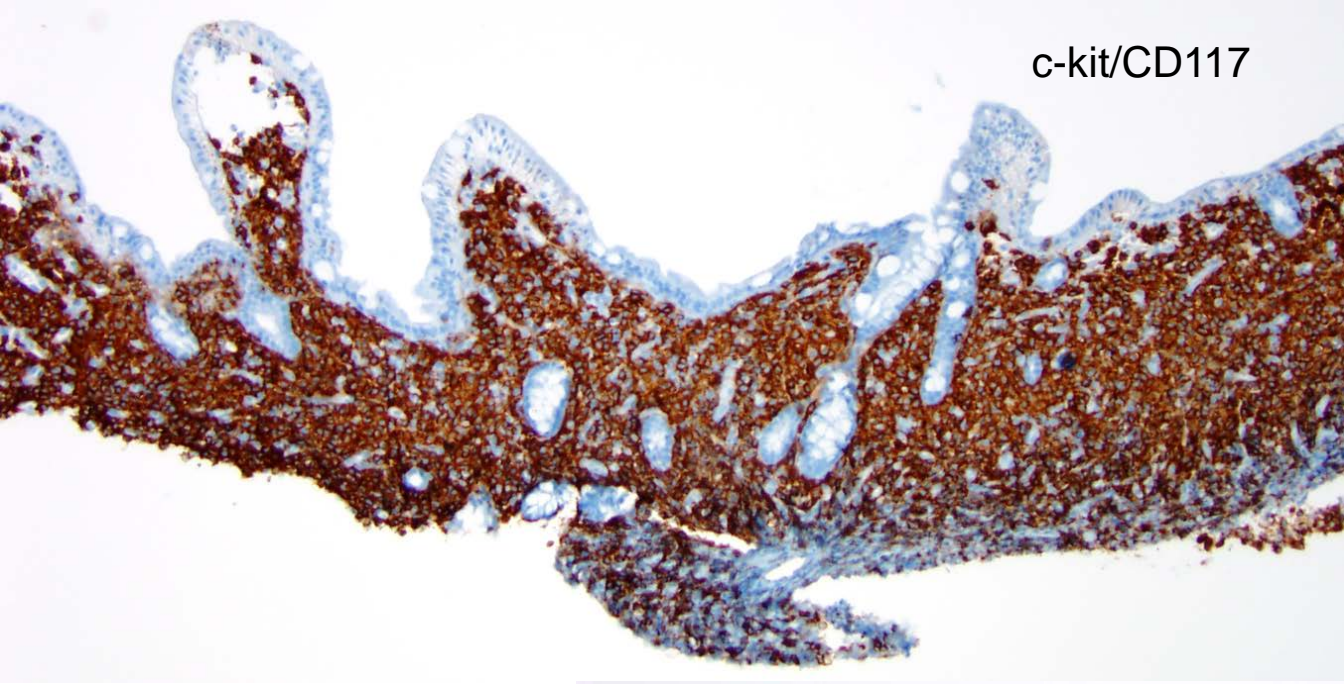
Other “faces” of mastocytosis in the GI tract



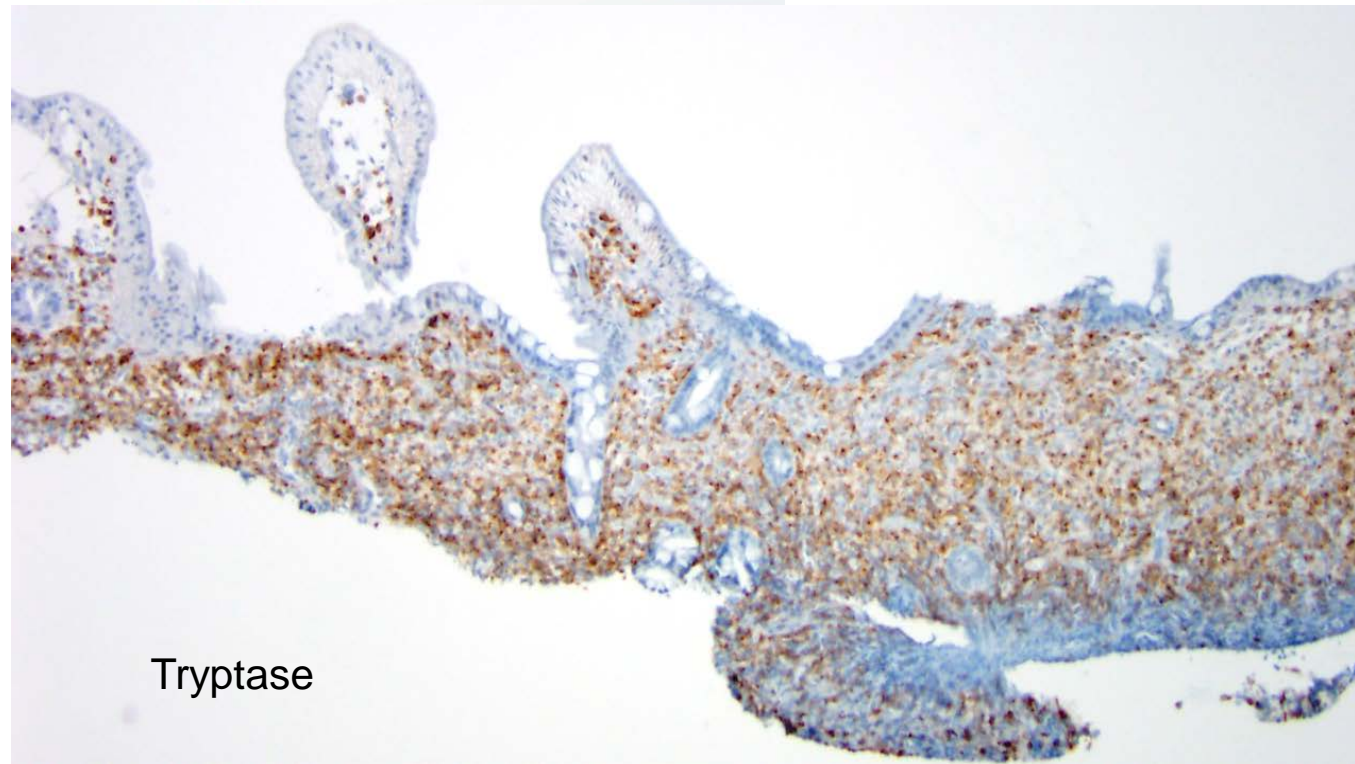




c-kit/CD117

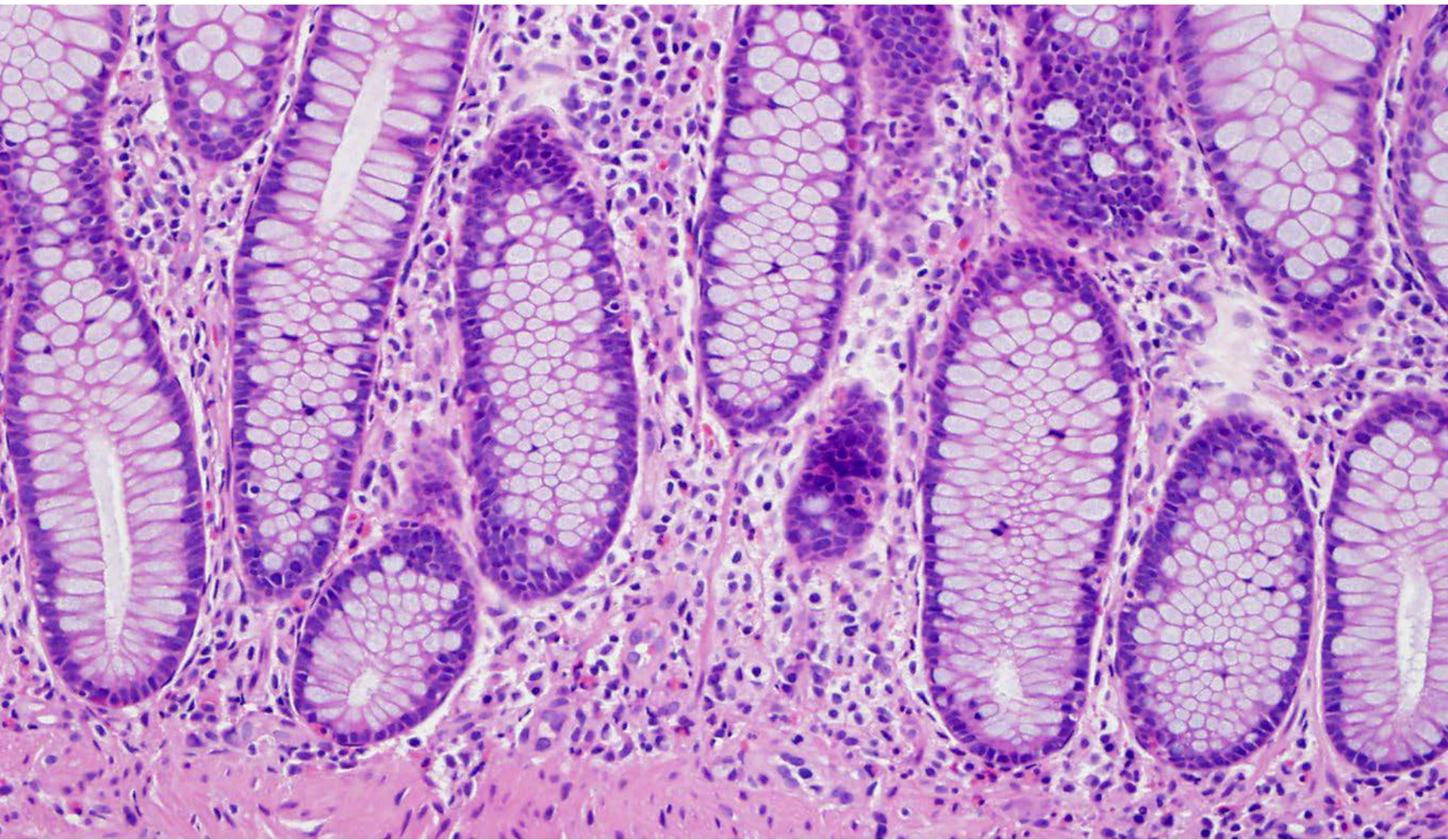


Tryptase

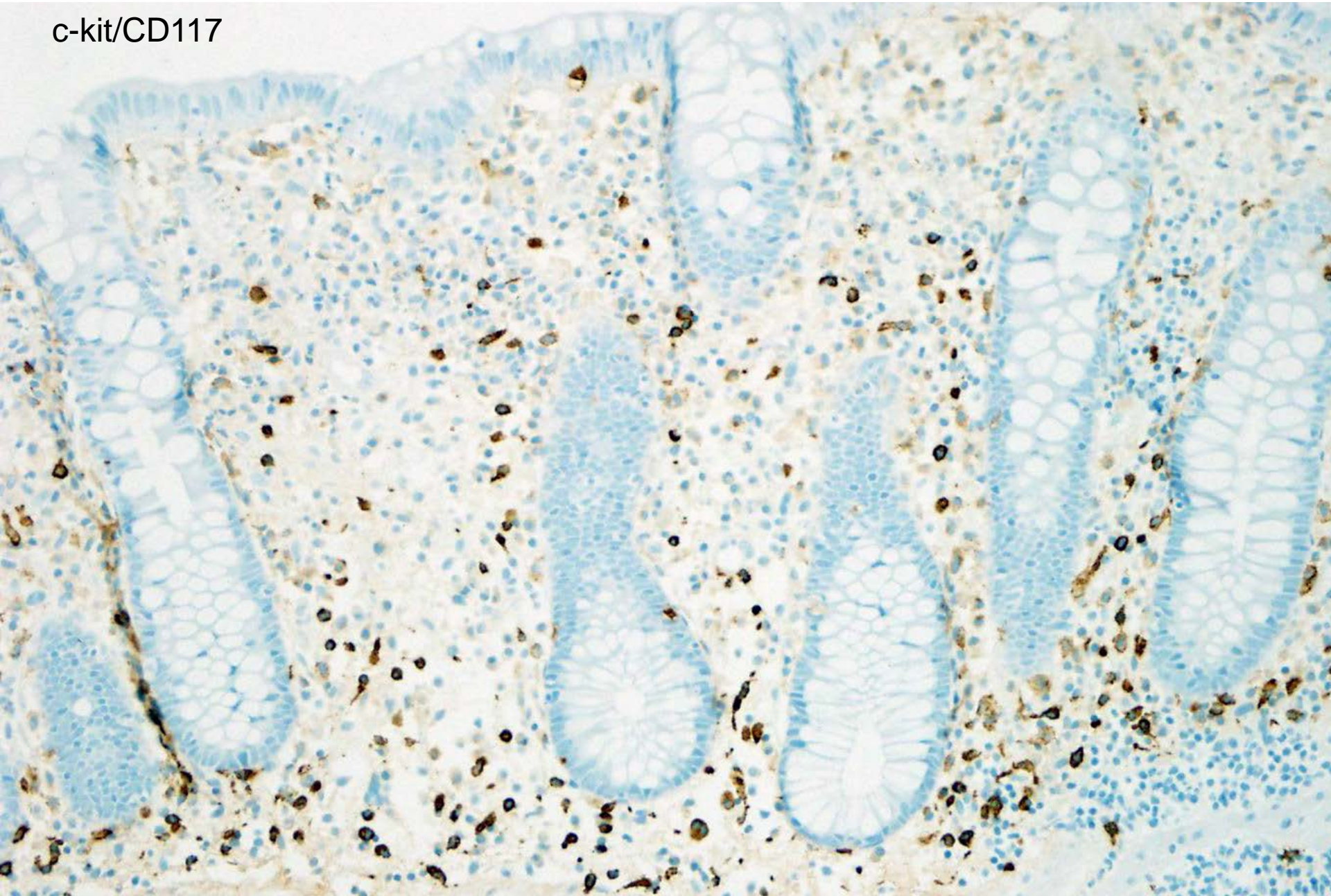




c-kit/CD117



c-kit/CD117



Systemic Mastocytosis

- Pearls
 - High index of suspicion essential
 - At low magnification, can mimic chronic colitis
 - Use BOTH c-kit and tryptase stains (latter may have high background in GI tract)
 - *Potential pitfall*: Beware expression of macrophage/histiocyte markers (e.g., CD68)
 - Aberrant expression of CD25 helpful
- Recent study
 - Atypical mast cell infiltrates limited to the GI mucosa may not merit a label of “systemic mastocytosis”
 - Aggregates of CK117/CD25+ mast cells in GI mucosae
 - No other suspicion of mastocytosis
 - Patients had GI symptoms that *spontaneously resolved*

Johncilla M, et al. *Am J Surg Pathol.* 2018;42(10):1390-1395

Mast Cell Activation Syndrome(MCAS)

Criteria

1. Episodic symptoms consistent with mast cell mediator release affecting ≥ 2 organ systems
 - Skin: urticaria, flushing, angioedema
 - GI: N/V, diarrhea, abdominal cramping
 - CV: hypotensive syncope or near syncope, tachycardia
 - Respiratory: wheezing
 - Naso-ocular: pruritus, nasal stuffiness
2. A decrease in frequency/severity/resolution of symptoms with antimediator therapy
3. Documented improvement in serum marker, preferably tryptase level
4. Rule out primary and secondary causes of mast cell activation

MCAS classified as an idiopathic disorder

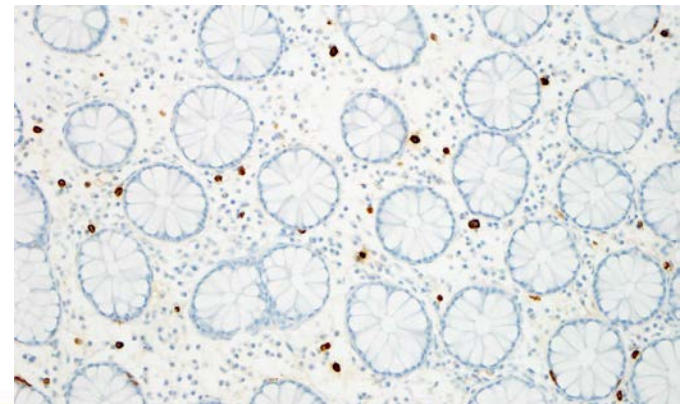
In some MCAS mast cells appear to be clonal

Mast Cell Activation Syndrome(MCAS) vs Systemic Mastocytosis

Bottom line.....

MCAS patients do not meet criteria for diagnosing mastocytosis

There are no definite histological findings (e.g., increased numbers of mast cells) in MCAS



Summary

Mast cell activation disease is a broad category that includes systemic mastocytosis

All of these diseases have clinical criteria for diagnosis, but only the various forms of mastocytosis have well-defined histopathological criteria

Adapted from Horny H-P, et al. Evaluation of mast cell activation syndromes: impact of pathology and immunohistology. *Int Arch Allergy Immunol.* 2012;159:1-5

Important information

Urticarial skin lesions

KIT mutation status

Serum tryptase (esp. >20-25 ng/mL)

Signs of allergy/anaphylaxis

Serum IgE

Hepatosplenomegaly

Lymphadenopathy

Ascites, elevated alk. phos. or LDH

Peripheral blood counts

GI symptoms

Bony changes

Thank you!