Mast Cell Activation Syndrome

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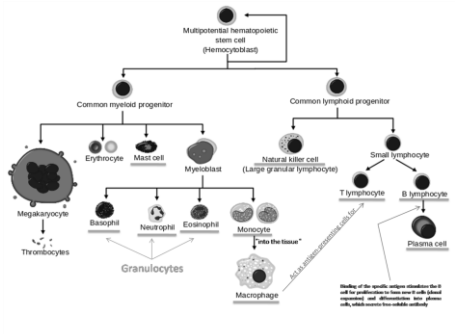
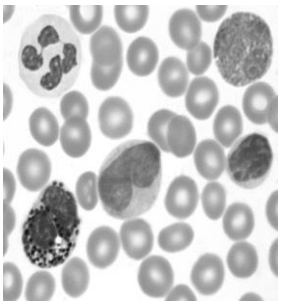
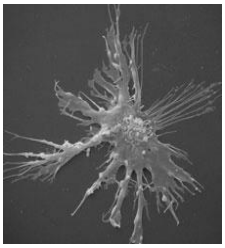
Objectives

1. Review functions of cells of the immune system.
2. Describe how mast cells are involved in immunity, type I hypersensitivity, and mast cell activation disease.
3. Differentiate the mast cell activation diseases mast cell leukemia, systemic mastocytosis and mast cell activation syndrome.
4. Evaluate a case study of mast cell activation disease by correlating clinical presentation and laboratory testing data.

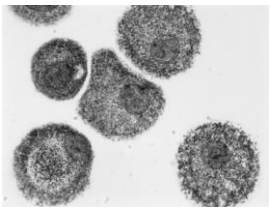






Good guys or bad guys?

Mast Cells



Allergic Reactions

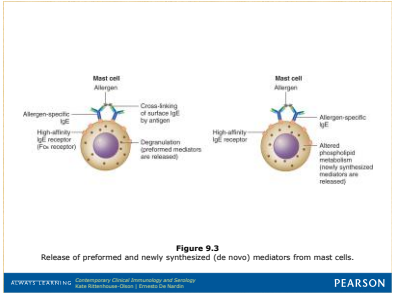


Figure 9.3
Release of preformed and newly synthesized (de novo) mediators from mast cells.

Urticaria

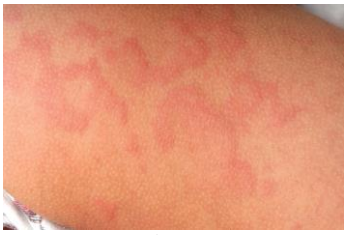


Figure 9.4
Uticaria, a skin rash caused by type I hypersensitivity.
Source: Levent Konuk/Shutterstock.com.

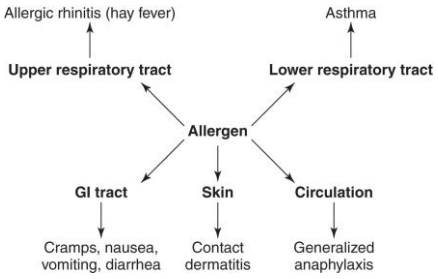


Figure 9.1
Hypersensitivity reactions and different target organs.

Mast Cell Mediators

Preformed Mediators of Mast Cells

Mediator	Action(s)
Histamine ECF-A	Increased permeability of capillaries; contraction of smooth muscle
Serotonin	Increased permeability of capillaries; contraction of smooth muscle
HMW-NCF	Recruitment of neutrophils
Proteases (eg, tryptase)	Degradation of basal membranes; cleave complement proteins

(a)

Newly Synthesized Mediators of Mast Cells

Mediator	Action(s)
Leukotrienes (C, D, and E)	Increased permeability of capillaries; contraction of smooth muscle
Platelet-activating factor (PAF)	Platelet aggregation; contraction of smooth muscle
Prostaglandin D2	Constriction of bronchial smooth muscle
Cytokines (IL-4, -5, -6)	Many different actions

(b)

Mast Cell Activation Disease

- Mast Cell Activation Syndrome (MCAS)
- Systemic Mastocytosis (SM) defined by WHO criteria
  - Indolent systemic mastocytosis
  - Isolated bone marrow mastocytosis
  - Smoldering systemic mastocytosis
  - Systemic mastocytosis with an associated clonal hematologic non-mast cell lineage disease
  - Aggressive systemic mastocytosis
- Mast Cell Leukemia (MCL)

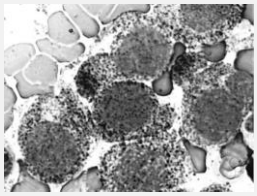
Molderings, G. J., Brettner, S., Homann, J., & Afrin, L. B. (2011). Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. *Journal of Hematology & Oncology*, *4*, 10. http://doi.org/10.1186/1756-8722-4-10

Current Classification

- Primary mast cell disorders
  - Mastocytosis (systemic and cutaneous)
  - Monoclonal mast cell activation syndrome
- Secondary mast cell disorders
  - Allergic disorders
  - Physical urticarias
  - Mast cell activation associated with chronic inflammatory or neoplastic disorders
- Idiopathic mast cell disorders
  - Idiopathic anaphylaxis
  - Idiopathic urticaria
  - Idiopathic histaminergic angioedema
  - Idiopathic mast cell activation syndrome

https://www.uptodate.com/contents/mast-cell-disorders-an-overview#H1309754785

Mast Cell Leukemia

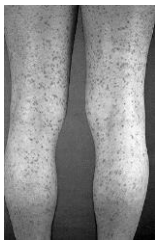


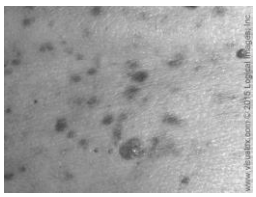
- ≥ 20% mast cells in bone marrow
- Mast cells found in increased number in peripheral blood
- Rapidly progressive affecting the liver, bone marrow and other organs
- Poor prognosis

Systemic Mastocytosis

- Characterized by organs infiltrated with mast cells
  - Bone marrow, liver, gastrointestinal tract, skin, other
- Several types, all rare, with a wide range of severity
- Episodes of symptoms caused by mast cell mediator release
  - flushing, abdominal cramping, hypotension, anaphylaxis

Urticaria Pigmentosa





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Mast Cell Activation Syndrome

- Recognized as a mast cell disorder in 2007
- Presents in adults with recurrent and episodic symptoms of mast cell activation similar to patients with SM
  - Flushing
  - Abdominal cramping
  - Hypotension
- Do ***not*** have urticaria pigmentosa
- Normal or only mildly elevated serum tryptase

Laboratory Testing

- CBC
- Liver Function tests
  - ALT
  - AST
  - ALP
- Tryptase (serum)
- Prostaglandin D_2 (PGD_2) (or its metabolite 11-beta-prostaglandin $F_{2\text{-alpha}}$ [$PGF_{2\text{-alpha}}$])
- *KIT* mutational analysis of peripheral blood or bone marrow
- Bone Marrow aspiration and biopsy

Other diagnostic testing

- Bone density studies
- Gastrointestinal studies including biopsies
- Skin biopsies
- Imaging studies of affected organs

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).

Reproduced with permission from: Horny HP, Metcalfe DD, Bennett JM, et al. Mastocytosis. In: WHO classification of tumours of haematopoietic and lymphoid tissues, 4th ed, Swerdlow SH, Camp E, Harris NL, et al (Eds), IARC, Lyon 2008.

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Comparison of clinical and diagnostic features for systemic mastocytosis, mast cell activation syndromes, and idiopathic anaphylaxis

	Systemic mastocytosis	Monoclonal mast cell activation syndrome (MMAS)	Idiopathic mast cell activation syndrome (IMCAS)	Idiopathic anaphylaxis
Baseline tryptase*	>20	Normal or mildly increased	Normal or mildly increased	Normal
hR D816V	+	+	–	–
Multifocal mast cell aggregates in the bone marrow	+	–	–	–
Aberrant CD25 on bone marrow and other non-cutaneous mast cells	+	+	–	–
Urticaria pigmentosa	+/–	–	–	–
Mediator-release symptoms	+	+	+	+
Hypotensive episodes	+/–	+/–	+/–	+/–
Urine N-MH or PGD_2	Increased at baseline	Increased during symptoms	Increased during symptoms	Increased during symptoms
Response to antimediator therapy	+	+	+	+/–

N-MH: N-methylhistamine; PGD_2: prostaglandin D_2.

* Elevations in serum tryptase corresponding to symptoms (particularly hypotension) may be seen in all four disorders. Increases in tryptase greater than 1.2 x baseline value + 2 ng/mL are considered significant. For example, if a patient's baseline total tryptase was 5 ng/mL, a value of 8 ng/mL would represent a significant increase.

Modified from: Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: Proposed diagnostic criteria. J Allergy Clin Immunol 2010; 126:1099.

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Common Triggers

- Insect stings and venom
- Drugs
  - Aspirin and other NSAIDs
  - Narcotic analgesics (e.g. codeine, morphine)
  - Antibiotics
- Changes in temperature (heat and cold)
- Mechanical irritation (massage, friction, pressure)
- Emotional stress
- Spicy and histamine-rich foods
- Alcohol
- Exercise
- Infections
- Fever

MCAS implicated in common disorders

- Interstitial cystitis
- Fibromyalgia
- Inflammatory bowel disease
- Irritable bowel syndrome

Symptoms

- Abdominal pain, intestinal cramping and bloating, diarrhea and/or constipation, nausea
- Chest pain
- Burning mouth pain
- Cough, asthma, dyspnea
- Rhinitis, sinusitis, conjunctivitis
- Splenomegaly
- Lymphadenopathy
- Tachycardia

Symptoms (2)

- Blood pressure irregularity
- Syncope
- Flushing
- Headache
- Neuropathic pain
- Neuropathy
- Decrease attention span, difficulty concentrating, forgetfulness
- Anxiety
- Insomnia

Symptoms (3)

- Vertigo
- Tinnitus
- Hives, pruritis
- Angioedema
- Muscle pain
- Bone pain
- Migratory arthritis
- Interstitial cystitis
- Fatigue
- Fever
- Environmental and chemical sensitivities

Treatment

- Not cured but managed
- First tier is avoidance of known triggers
- H1-histamine receptor antagonists
- H2-histamine receptor antagonists
- Cromolyn sodium
- Vitamins C and D
- Ketotifen

Treatment (2)

- Prednisone
- Cyclosporine
- Methotrexate
- Azathioprine
- Epinephrine

Mast Cell Activation Syndrome: A Case Study

Patient History

- In May 2014 a 29-year-old female consulted an allergist at Mayo Clinic in Rochester, Minnesota
- Ten years of episodes of flushing, swelling, nausea, severe abdominal pain, muscle and joint pain, chemical sensitivity, migraines, asthma, anaphylaxis and other symptoms
- Symptoms had increased in severity and frequency since 2011 following the birth of her second child

Patient History (2)

- Patient had consulted several local physicians
  - Family practitioner
  - Gastroenterologist
  - Allergist
  - Rheumatologist
  - Medical doctor practicing integrative medicine
  - Doctor of naturopathic medicine
- Patient rarely left her home and wore a mask when she did to avoid environmental triggers
- Adhered to a very rigid diet low in histamine prescribed by a nutrition therapist

Physical Examination

- Unremarkable with no skin rashes, urticaria or eczema
- Referred to a dermatologist for hyperpigmented lesion on abdomen
  - Reported mild dermatographic urticaria
  - Performed punch biopsy of right lateral thigh and found no evidence of urticaria pigmentosa (cutaneous mastocytosis)
- Referred to gastroenterologist
- Referred to psychiatrist

Laboratory Findings

- CBC, CMP, ESR, TSH, Calcitonin
- Immunoglobulins, SEP
- Urine chemistries
  - Creatinine
  - N-methylhistamine
  - Metanephrines
  - Beta prostaglandin F2-alpha
  - Zonulin-diamine oxidase/histamine
  - Amino acids
  - 5-HIAA
- JAK2 V617F
- Serum tryptase
- Mast cell tryptase stain

Mayo Clinic

Thursday, May 29, 2014
Mayo Clinic Trip: Diagnosis Edition

I went out on a limb. I prayed for answers. And God delivered.

After *years* of bewildering symptoms, I was given a *name*.

A name is such a gift. Your insides never feel quite settled when you don't know how to identify a thing. A name says, "You're not crazy. You are not alone." These are comforting truths when the disease is isolating and causes you to question your own sanity.

http://melissakeaster.blogspot.com/2014/05/mayo-clinic-trip-diagnosis-edition.html

"After almost ten years of suffering and an earnest, two-year-long quest for diagnosis, Dr. Park told me on May 27, 2014, I have Mast Cell Activation Disease (MCAD)."

Conclusion

- Patient was diagnosed with mast cell activation syndrome
- Prescribed several medications
  - Zyrtec 10 mg twice a day
  - Zantac 150 mg twice a day
  - Singulair 10 mg once a day
  - Gastrocrom (cromolyn sodium) would be prescribed if this regimen proved to be unhelpful
  - Doxepin would be considered as a possible next drug

Conclusion (2)

- Unable to tolerate antihistamines
- Gastrocrom 3x per day helped with gastrointestinal symptoms
- After brief remission, patient became increasingly sensitive to smells undetectable to others
- Exposure to heat and cold, as well as other triggers caused episodes of debilitating neurological impairment

References

- Hamilton, Hornick, Akin, Castells & Greenberger. (July 2011). Mast cell activation syndrome: A newly recognized disorder with systemic clinical manifestations. *The Journal of Allergy and Clinical Immunology.* Retrieved June 21, 2016, from http://www.jacionline.org/article/S0091-6749(11)00675-0/fulltext
- Theoharides, Valent & Akin. (July 2015). Mast cells, mastocytosis, and related disorders. *The New England Journal of Medicine.* Retrieved June 21, 2016, from http://www.nejm.org/doi/full/10.1056/NEJMra1409760
- Molderings, Brettner, Homann & Afrin. (March 2011). Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. *Journal of Hematology & Oncology.* Retrieved June 21, 2016, from http://jhoonline.biomedcentral.com/articles/10.1186/1756-8722-4-10
- Krystel-Whittemore, M., Dileepan, K. N., & Wood, J. G. (2015). Mast Cell: A Multi-Functional Master Cell. *Frontiers in Immunology*, *6*, 620. http://doi.org/10.3389/fimmu.2015.00620. Retrieved October 9, 2016.
- https://www.uptodate.com/contents/mast-cell-disorders-an-overview#H1309754785
- De Nardin, E. & Rittenhouse-Olson, K. (2013) Hypersensitivity Reactions. *Contemporary clinical immunology and serology.* Pearson Education, Inc.
- http://melissakeaster.blogspot.com
- Melissa Keaster's medical records obtained by patient's permission