Angioedema

ALLERGY & IMMUNOLOGY FELLOWS:
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Outline

- Case Presentation
- Angioedema
  - Clinical Features
  - Evaluation: history, physical exam, labs
  - Pathophysiology & Treatment
    - Mast cell mediated
    - Unknown
    - Bradykinin mediated
- Case Discussion

Case Presentation

- CC: angioedema
- HPI:
  - 58 yr old male presents to allergy and immunology office for angioedema. Two weeks ago had an episode of angioedema.
  - 2PM started with upper lip swelling and took children's dose Benadryl.
  - Woke up 11:30PM and lip got bigger so he took another children's Benadryl.
  - Then 1:30AM lip got more swollen so he went to the ER.
  - In ER, he was given steroid and Benadryl but continued to swell, so then IM Epi was administered. He was discharged 24-36 hours later.
  - Medication at discharge: prednisone 10mg daily, pepcid and claritin
  - Upon further questioning: at noon that day he had some Cheetos and Gatorade but has eaten these foods in the past without any reactions.
  - No illness at time of reaction, no new meds
  - He had hives as a kid with increased body temp and in the grass but never had hives as an adult
  - No history of swellings without hives

Case Presentation

- PMHx:
  - Seasonal allergies
  - Food allergy: fish (able to eat shellfish)
  - Diverticulitis
- PSHx:
  - None
- FamHx:
  - Allergic rhinitis: brother, sister
- SocHx:
  - No tobacco
- Allergies: NKDA
- Meds:
  - Prednisone 10mg po daily
  - Pepcid 20mg po daily
  - Claritin 10mg po daily

Case Presentation

- Vitals:
  - Weight: 186lbs Height: 5'8" BP: 130/79
- PE:
  - **General:** No acute distress, comfortable, oriented
  - **Eyes:** Conjunctiva and sclera normal without injection
  - **Ears:** TM's normal with normal landmarks; external auditory canals normal without erythema or exudate
  - **Nose:** Septum midline, no turbinate edema, no discharge
  - **Neck:** Supple; no cervical lymphadenopathy; no masses; thyroid normal
  - **Oropharynx/Throat:** Moist mucosa without lesions or exudate
  - **Chest wall:** Symmetric, non-tender, no deformities
  - **Lungs:** Bilaterally clear to auscultation without wheezes, rhonci, or rales; no cough; good air exchange
  - **Heart:** Regular rhythm, no murmurs, no gallop
  - **Extremities:** No cyanosis, clubbing, or edema; no joint erythema, swelling, or tenderness
  - **Skin:** No rash, no lesions; no purpura; no petechiae

Clinical Features

- Following anatomic sites can be affected:
  - Face, lips, mouth, throat, larynx, uvula, tongue, extremities, genitalia, bowel wall
  - Skin and mucous membranes
- Asymmetric distribution

Clinical Features

- With mast cell mediated
  - Urticaria, flushing, generalized pruritus, bronchospasm, throat tightness, hypotension
  - Onset in minutes to hours and spontaneous resolution in hours to a few days
- With bradykinin mediated
  - No urticaria, bronchospasm or other symptoms of allergic reactions
  - Longer timeline
    - Develops over 24-36 hours and resolves in 2-4 days

Evaluation: History

- Exposure history preceding symptoms
  - Unusual exposures, activities, foods
  - Medications?
    - NSAIDs, ACE-I, ARB, estrogens
  - Family history

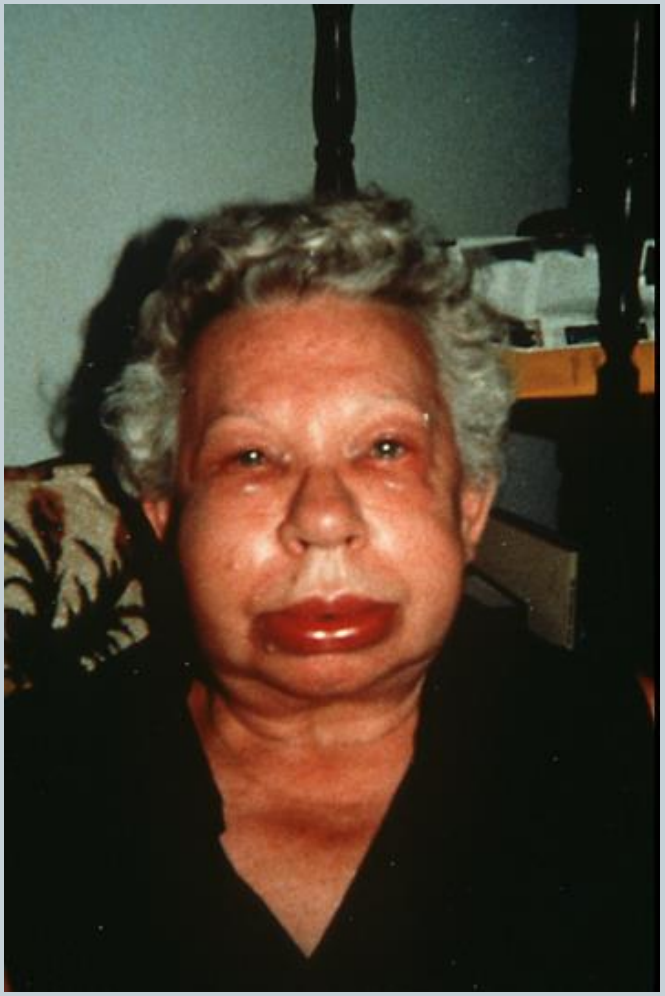
Evaluation: Physical Exam

- Angioedema
  - Usually of the skin or mucous membranes of the upper respiratory or GI tract
  - Asymmetrical
  - Nonpitting
  - Skin color – normal or slightly erythematous
- Are there hives, flushing, pruritus, bronchospasm, throat tightness or hypotension?

Evaluation: Labs

- CBC with differential
- Complete metabolic panel
- CRP, ESR
- C4 levels
- Depending on history:
  - Urinalysis
  - Serum tryptase (marker of mast cell activation, but does not rule out)
  - C3 levels, C1 inhibitor (serum level and function)
  - ImmunoCAP (specific IgE): in cases of suspected allergy
  - Abdominal CT: in cases of intestinal angioedema

Angioedema Pictures



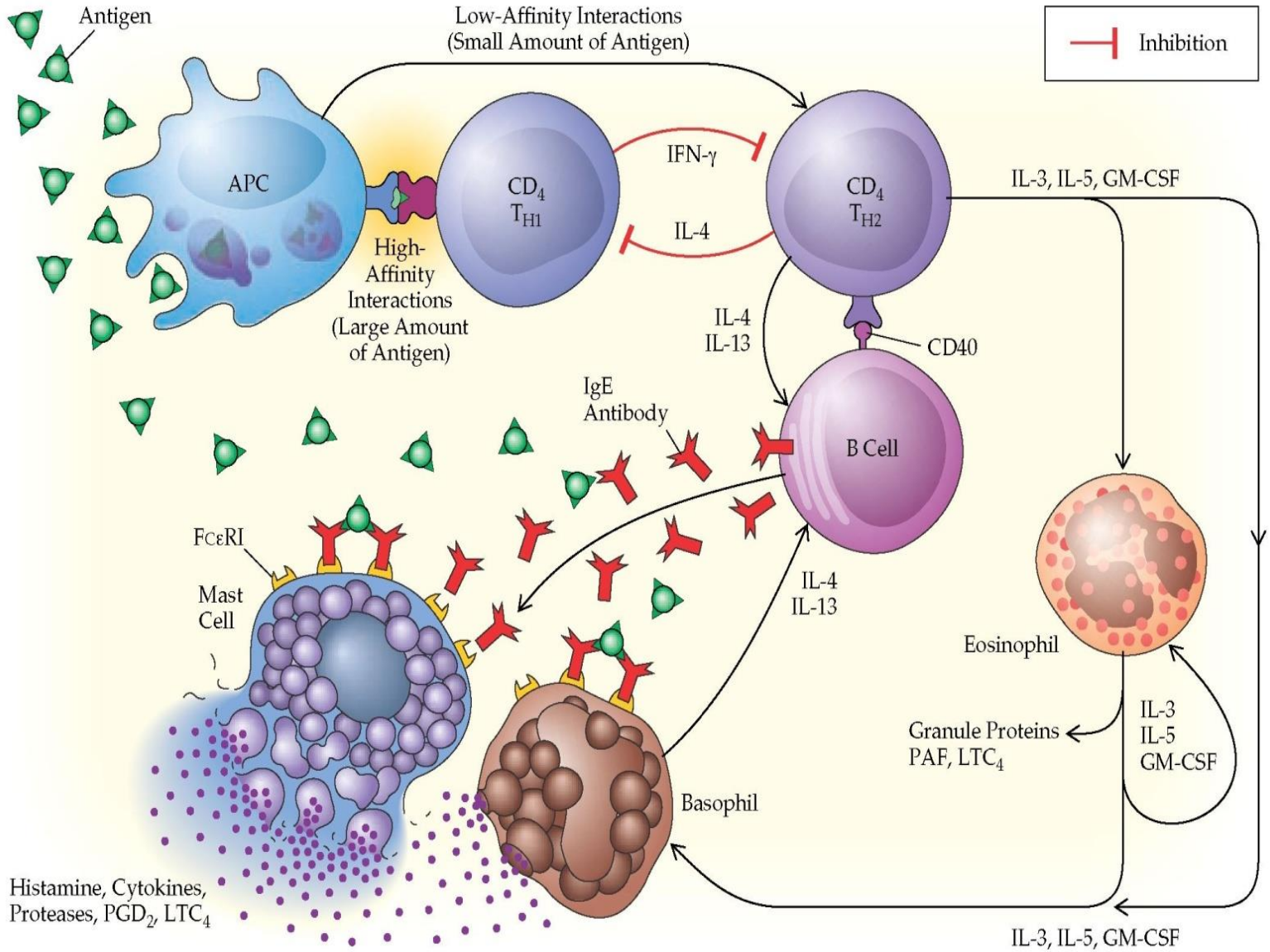
Causes

- Mast Cell Mediated
  - IgE mediated allergic reactions
  - Direct mast cell mediator release
  - Alterations in arachidonic acid metabolism with mast cells
- Etiologies of unknown
  - Idiopathic angioedema
  - Infections
  - Drugs
  - Hypereosinophilic syndrome
  - Urticarial Vasculitis

Mast Cell Mediated

- Allergic or Anaphylactic reactions
  - Type 1 hypersensitivity (IgE)
  - Many triggers
    - Foods, drugs, insect stings, latex
  - Occurs within minutes to 2 hrs following exposure
  - Potentially fatal
    - Treatment consists of epinephrine

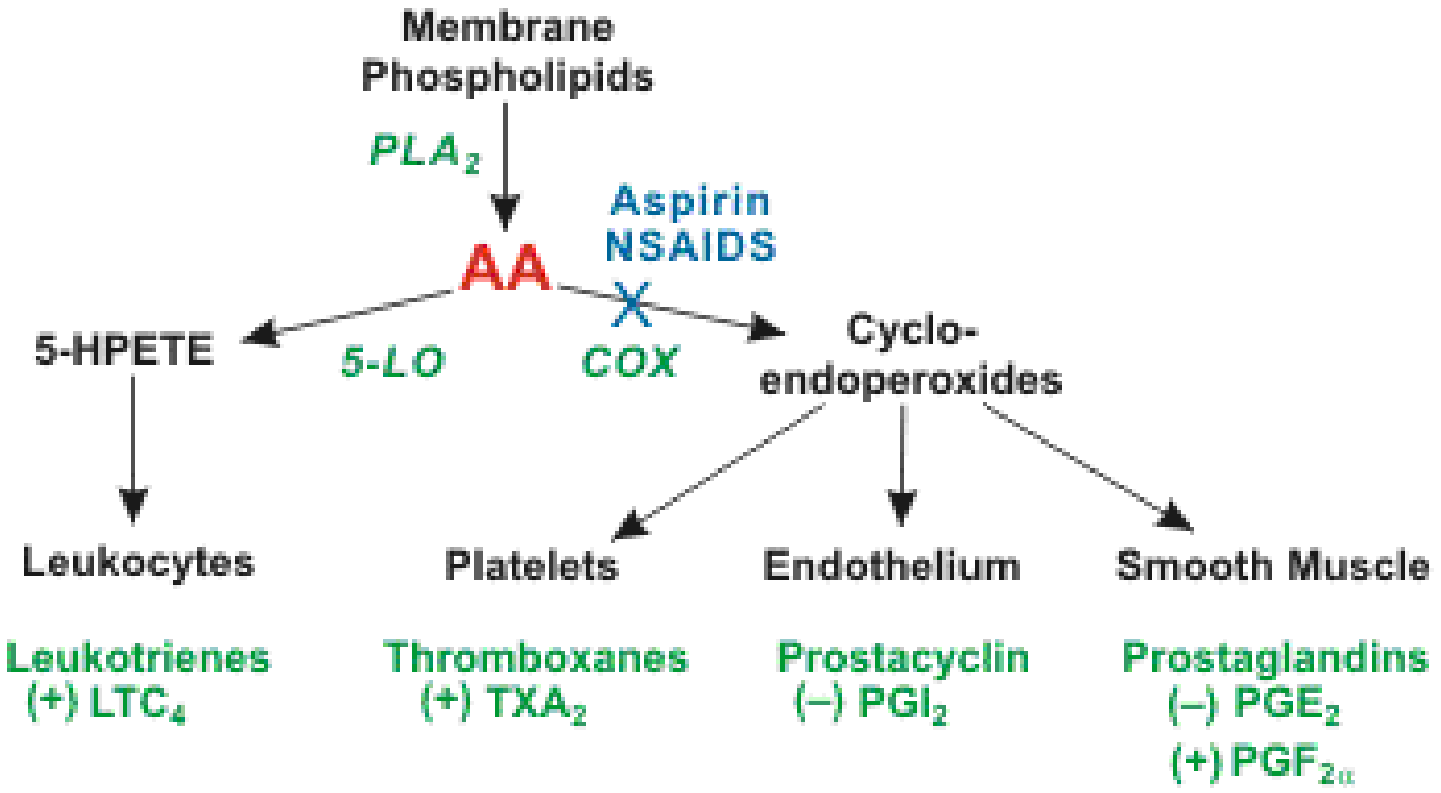
- Direct mast cell release
  - Opioids
  - Radiocontrast agents
  - Muscle relaxers



http://www.nature.com/nrd/journal/v1/n1/images/nrd702-f1.gif

Mast Cell Mediated

- Arachidonic acid metabolism
  - ASA, NSAIDs
  - Inhibition of cyclooxygenase 1
    - Formation of prostaglandins from AA
    - Increased proinflammatory mediators
  - Treatments
    - Epinephrine, avoidance, desensitization



Abbreviations: AA, arachidonic acid; PLA_2, phospholipase A_2; PLC, phospholipase C; COX, cyclooxygenase; NSAIDS, non-steroidal anti-inflammatory drugs; +, vasoconstriction; –, vasodilation.

http://www.cvphysiology.com/Blood%20Flow/AA%20metabolism.gif

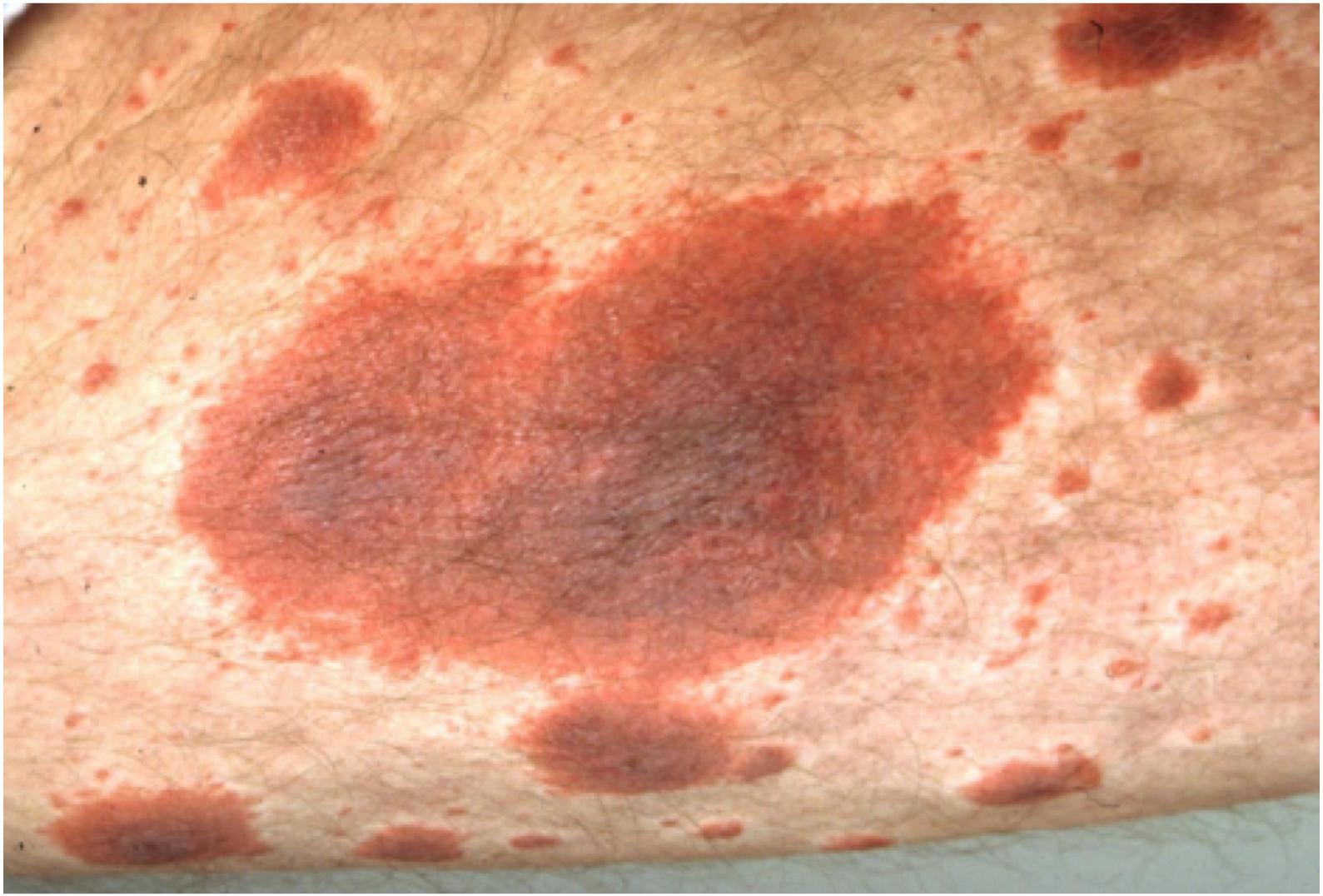
Unknown Mechanisms

- Idiopathic angioedema
  - With or without urticaria
- Infections
  - Children
  - Usually viral
- Drugs
  - Many classes of medications reported
  - CCB, SSRI, PPIs, Vaccines

Hypereosinophilic Syndome

- Overproduction of eosinophils
  - Eosinophilic infiltration
  - Overexpression of IL 5
  - 15% develop angioedema
  - Prednisone, Gleevac, Mepolizumab
- Gleich's Syndrome
- Urticarial vasculitis

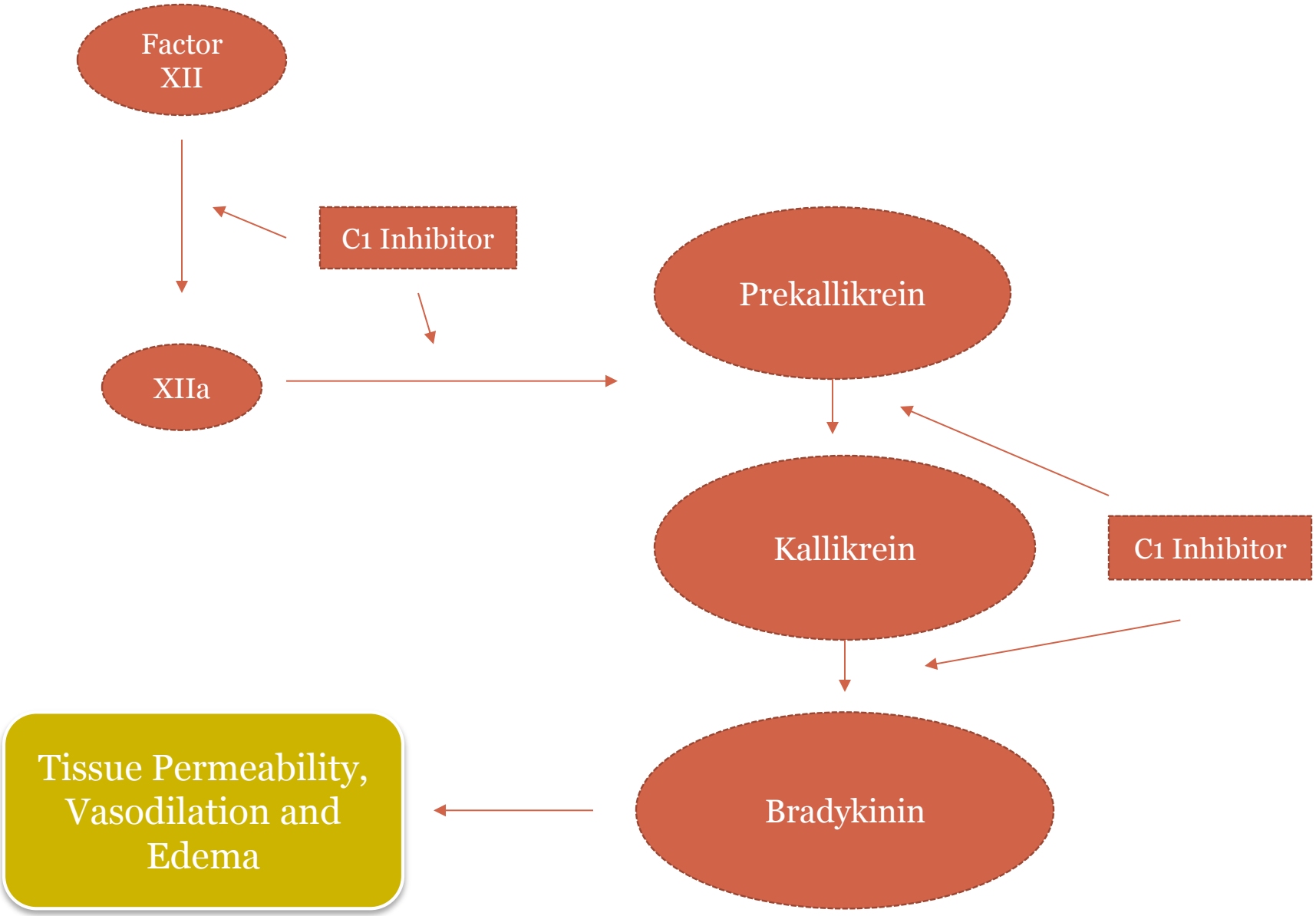
Urticarial vasculitis



Urticarial patch with central ecchymosis.

Bradykinin-Induced Angioedema

- Separate, non-allergic entity, where mast cells are not involved
- Mechanism
  - Bradykinin is a potent vasodilatory peptide which exerts its action on specific endothelial β2 receptors
  - During bradykinin-induced angioedema elevated levels of bradykinin (from increase production of decreased degradation) results in increased tissue permeability, vasodilation and edema


Factor XII
C1 Inhibitor
Prekallikrein
XIIa
Kallikrein
C1 Inhibitor
Bradykinin
Tissue Permeability, Vasodilation and Edema

Bradykinin-Induced Angioedema

- Clinical Features
  - Angioedema will often be indistinguishable from histamine-mediated angioedema
  - The secondary features, however, will be absent in Bradykinin-induced angioedema
    - Absence of urticaria & bronchospasm are distinguishing features
  - Timing of angioedema may also help in differentiating
    - Onset and duration usually more prolonged, with angioedema developing over 24-36 hours and lasting 2-4 days
    - Often the trigger and onset of angioedema not apparent (i.e. ACE-I induced angioedema can develop weeks to years after first use)

Bradykinin-Induced Angioedema

- Differential Diagnosis
  - Can be separated based on hereditary and acquired causes
    - Hereditary Angioedema
      - Types I, II, III (HAE with normal C1 inhibitor level)
    - Acquired Angioedema
      - Acquired C1 Inhibitor Deficiency (i.e. Acquired Angioedema)
      - ACE-I Induced
      - Idiopathic angioedema

Bradykinin-Induced Angioedema

- Hereditary Angioedema
  - Characterized by low levels (type I) or nonfunctional (type II) C1 Inhibitor leading to inappropriate regulation of the Bradykinin pathway
  - Family history of angioedema will often be identified as a result of autosomal dominant inheritance patter
    - Types I and II – *SERPING1* mutation
  - Clinical Features
    - Recurrent angioedema episodes without urticaria or pruritis
    - Most often affects the upper respiratory and gastrointestinal tract
    - Cannot distinguish between the different types based on clinical presentation

Bradykinin-Induced Angioedema

- Hereditary Angioedema Type I
  - Makes up approximately 85% of all HAE cases
  - Characterized by low C1 INH levels
  - Diagnosis
    - C1 Inhibitor protein *Antigenic* and *Functional* levels will be decreased, low C4 levels
    - C1 INH Antigenic level range from undetectable to less than 30-50% of normal

- Hereditary Angioedema Type II
  - Makes up approximately 15% of all cases
  - Characterized by dysfunctional C1 INH
  - Diagnosis
    - Normal or increased C1 Inhibitor protein *Antigenic* level, Low C4 level
    - Low C1 Inhibitor *Functional* level

Bradykinin-Induced Angioedema

- Hereditary Angioedema with normal C1 Inhibitor (Type III)
  - Makes up very small percentage of all cases
  - Characterized by normal C1 INH levels and function
  - Family history of angioedema- possible gain-of-function mutation in Factor XII can be detected in a subset of patients
  - Diagnosis
    - Normal C1 Inhibitor protein *Antigenic* and *Functional* levels, normal C4 levels

Bradykinin-Induced Angioedema

- Hereditary Angioedema Treatment
  - C1 INH concentrate- mainstay of treatment
    - Prophylaxis-*Cinryze* (Human C1 INH) can be intravenously used for both short term and long term prophylaxis
      - Upcoming dental or surgical procedures may warrant short-term prophylaxis
      - Long-term prophylaxis indicated for those with frequent and severe attacks
    - Acute treatment-*Berinert* (Human C1 INH) IV, *Ecallantide & Icatibant* (Bradykinin antagonists) SQ
  - Attenuated Androgens- used for both short term and long term prophylaxis
  - Antifibrinolytics and FFP- rarely used

Bradykinin-Induced Angioedema

- Acquired C1 Inhibitor Deficiency (Acquired Angioedema)
  - Mechanism
    - Incompletely understood- depletion of C1 INH usually by B cell clonal proliferation
  - Clinical Features
    - Present in the fourth decade of life, which is the major distinguishing factor from HAE (>90% present before 20 yo)
    - Symptoms otherwise indistinguishable from HAE
  - Associated conditions- the majority of patients diagnosed with AAE are found to have an underlying disorder
    - 30-40% are found to have some type of malignancy (lymphocytic or other)
    - 30-40% are found to have monoglonal gammopathy of undetermined significance (MGUS)
    - 5-10% are found to have an autoimmune condition

Bradykinin-Induced Angioedema

- Acquired C1 Inhibitory Deficency (AAE)
  - Should be suspected in a patient with angioedema starting in the fourth decade without a family history of angioedema
  - Diagnosis
    - Low C4 level
    - Low or normal C1 Inhibitor protein *Antigenic* level
    - Low C1 Inhibitor *Functional* level
    - Low C1q levels
  - Initial C4 and C1 INH Antigenic and Functional levels can be drawn
    - If no family history and low C4 and C1 INH levels, C1q should be drawn to rule out AAE

Bradykinin-Induced Angioedema

- Acquired C1 Inhibitor Deficiency (AAE)
  - Once AAE is confirmed by laboratory testing, more extensive workup for malignancy and autoimmune conditions should be undertaken and may include hematology evaluation

Bradykinin-Induced Angioedema

- ACE-Inhibitor Induced Angioedema
  - Mechanism
    - Angiotensin Converting Enzyme is a peptidase that cleaves Bradykinin and Substance P into inactive peptides
    - ACE inhibition will lead to reduction of catabolism of Bradykinin which predisposes to angioedema episodes in some patients
  - Clinical Features
    - Angioedema attacks show a strong predilection for the face, lips and tongue
    - Bowel and extremity edema are not common
    - First episode most frequently occurs in the first month, however many experience attacks 6 months to years after initiation

Bradykinin-Induced Angioedema

- ACE-Inhibitor Induced Angioedema
  - Treatment
    - Primary treatment is discontinuation of medication
    - Airway management
    - Antihistamines, corticosteroids, and epinephrine are commonly used but have proven ineffective
    - Bradykinin antagonists (Icatibant, Ecallantide)

Case Discussion

- Plan after initial visit:
  - Stop prednisone, Claritin, and pepcid
  - If another event: IM epi and to ER
  - Can take Benadryl 50mg po prn
  - Labwork

Lab Results

Test Name	In Range	Out of Range	Reference Range		Lab
ANGIOEDEMA HEREDITARY ACQUIRED					
C4, SERUM		LESS THAN 2 L	16-47	MG/DL	P
C1 ESTERASE INHIBITOR,PROT		7 L	21-39	mg/dL	G
C1 INHIBITOR,FUNCTIONAL		46 L	>=68	%	G
Reference Range (%): >= 68 Normal 41-67 Equivocal <= 40 Abnormal For more information on this test, go to: http://education.questdiagnostics.com/faq/FAQ54.					
C1Q, SERUM		<3.6 L	5.0-8.6	MG/DL	F
Low levels of C1q indicate either increased consumption (catabolism) or decreased synthesis.					

Bradykinin-Induced Angioedema

	HAE	ACID	Idiopathic
C1-INH function	Low	Low	Normal
C1-INH antigen	Low (85%)	Low	Normal
C4	Low	Low	Normal
C1q	Normal	Low	Normal

Case Discussion

- Dx: acquired angioedema
- Repeat labs to confirm diagnosis
  - Labs sent out to National Jewish Hospital in Denver, colorado
- Prescribe Firazyr injection prn event
- Refer to hematology/oncology to rule out any underlying lymphoproliferative /autoimmune disorder

Thank You

- Questions?