

Urticaria and Angioedema

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Drew White, MD
Scripps Clinic
San Diego, CA



What is a hive?

- Pruritic, erythematous, cutaneous elevation of the skin that blanches with pressure. (dilated blood vessels and edema)



Urticaria or not?



Distribution

- Urticaria – virtually any part of the body
- Angioedema – not characteristic in dependent areas, asymmetrically distributed, transient
 - Face, tongue, extremities, genitalia





Acute Urticaria

- Most likely caused by allergic reaction to food, drug or viral infection
- Must differentiate from anaphylaxis
- Simple way is to identify another organ system which is affected (anaphylaxis)
- Or time course of urticaria



Acute Urticaria

- Seasonal pattern – occurs in atopic individuals (pollens etc.)
- Contact urticaria (dog lick)
- Drugs – can be immediate or up to 10 days later
- Foods – immediate, not a cause of chronic urticaria
- Viral illness

Bizarre Anaphylaxis #1

- Mosquito anaphylaxis



- Galindo, P A. Gomez, E. Borja, J. Feo, F. Garcia, R. Lombardero, M. Barber, D. Mosquito bite hypersensitivity. *Allergologia et Immunopathologia*. 26(5):251-4, 1998 Sep-Oct

Chronic vs Acute Urticaria

Urticaria > 6 weeks = chronic

Chronic urticaria very unlikely to establish cause

Approx 90-95% patients with chronic urticaria have no identifiable cause

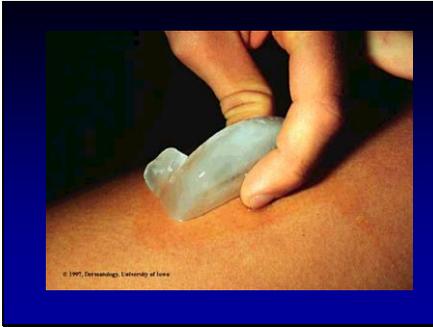
Physical Urticarias

- Triggered by environmental factors
- Dermatographism is most common affecting 2-5% of the general population
 - Trauma induced reaction causing histamine release
- Abnormal circulating factor confers pressure sensitivity to dermal mast cells.

Cholinergic urticaria

- 1-3mm wheals surrounded by erythematous flares
- Seen after increase in core body temp commonly in young adults
- Develop after strenuous exercise, hot bath, emotional stress
- Progression to exercise induced anaphylaxis is reported





Delayed Pressure Urticaria

- Swelling 4-6 hours after pressure applied to skin
- Palms, soles, buttocks commonly involved
- Other symptoms include malaise, fever, chills, arthralgias, headache, leukocytosis
- Poor response to antihistamines
- Can accompany chronic idiopathic urticaria

Cold Urticaria

- Urticaria may develop within minutes on areas directly exposed to cold or on rewarming
- Ingestion of cold water → lip swelling
- Death has been reported with swimming, diving or whole body immersion



Solar Urticaria

- Urticaria develops within 1-3 minutes of exposure to light
- Lesions last 1-3 hours
- Six subtypes which are triggered by specific wavelengths of light

Bizarre Anaphylaxis #2

- Triatoma Anaphylaxis

- Moffitt JE, Venarske D, Goddard J.
- Yates AB, deShazo RD. Allergic reactions to *Triatoma* bites.
- *Annals of Allergy, Asthma, & Immunology*. 91(2):122-8; 2003 Aug.



H. pylori

- Systematic Review:
- Critical review of the 10 positive studies leads to an overall low grade for this intervention.
- 9 completely negative studies
- “evidence that H. pylori eradication leads to improvement in chronic urticaria is weak and conflicting....”
- Shakouri et al, *Curr Opin Allergy Clin Immunol* 2010

Mechanisms



Case Report

- 43 yo male allergist at Scripps Clinic
- 5/07 developed R L5 dermatome zoster
- At this same time developed persistent urticaria without angioedema
- Responded well to cetirizine 10mg daily, but recurs >36hrs without dose
- Went into remission 5/08

Disproven

- Psychophysiologic reactions
- Food allergies
- Adverse reactions to food additives
- Cutaneous fungal infections (id reactions)
- H. pylori (for the most part....)

What do you think is going on?

- Chronic VZV infection?
- Zoster and CU totally unrelated?
- Zoster somehow changed the functionality of basophils and mast cells?
- Zoster (through molecular mimicry) led to autoimmune IgG to mast cell/basophil?

FIG 3. Tissue factor immunoreactivity in urticarial skin lesions. **A:** Skin control skin. **B:** Urticarial skin. Immunohistochemical analysis of paraffin-embedded skin. **Urticaria skin lesions display a strong expression of tissue factor by mast cells (immunoreactivity with IgG as a control is normal skin. Immunoreactivity control skin appears to be immunoreactivity negative for tissue factor).**

FIG 4. Bar graph of tissue factor immunoreactivity in urticarial skin lesions. The y-axis is labeled 'Tissue Factor Index' and ranges from 0 to 10. The x-axis is labeled 'Control skin' and 'Urticaria skin'. The bar for 'Control skin' is at approximately 1, and the bar for 'Urticaria skin' is at approximately 8.5.

Tissue Factor Immunoreactivity in CU
Aono et al, *J Allergy Clin Immunol* 2007;119:705-10.

Workup for Chronic Urticaria

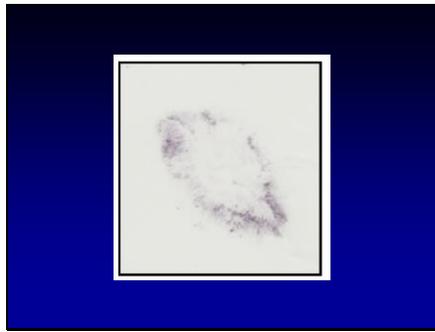


Table II. Principal cutaneous diseases that can manifest with urticarial lesions

Common	
Urticarial dermatitis	Contact dermatitis (irritant or allergic)
Arthropod bite reactions	Exanthematous drug eruption
Mastocytosis (children)	Autoimmune bullous diseases
Subepidermal—bullous pemphigoid, gestational pemphigoid, linear IgA dermatosis, epidermolysis bullosa acquisita, and dermatitis herpetiformis of Duhring	Intraepidermal—pemphigus herpetiformis
Pruritic urticarial papules and plaques of pregnancy	Small-vessel vasculitis (urticarial vasculitis)
Rare	
Autoimmune progesterone/estrogen dermatitis	Intestinal granulomatous dermatitis
Eosinophilic cellulitis (Wells syndrome)	Neutrophilic eccrine hidradenitis
Urticaria-like follicular mucinosis	

Bizarre Anaphylaxis #3

ABC News....

- "...Fifteen-year-old Christina Desforges of Saguenay, Quebec, died last week after kissing her boyfriend, who had eaten a peanut butter sandwich hours earlier. He passed along traces of peanuts to Desforges, who was severely allergic, and she immediately became short of breath. She was given a shot of adrenaline to counteract the symptoms, but that did not help. She died of respiratory failure in a Quebec City hospital."

2 Strategies

- History and physical
- CBC, ESR, LFT's, P2, Complement, Cryoglobulin
- RF, ANA, dsDNA
- Hep B, RPR, ASO, Strongyloides, UA
- RAST for inhalants, foods, IgE
- stool for O+P, occult blood
- Throat culture, vaginal swab for candida
- CXR, sinus x ray, dental films
- Skin biopsy
- Provocation for physical urticaria
- All drugs changed to alternative
- Elimination diet (salicylates, dyes, benzozites, sorbic acid, sodium glutamate, sulfites, antioxidants, sodium nitrate, parabens, vasoactive amines, histamine liberators, sugar, yeast, spices, coffee, crustaceans, fish, meat, eggs, milk, potato x 3 weeks
- Oral food or drug rechallenge when indicated.

- 220 patients
- Bottom line, 1 patient with a parasitic infection, not suspected by the dermatologist would have been picked up.

• Kozel MM. Arch Dermatol 1998;134:1575-1580

How NOT to practice allergy

- 25 yo male presents to the allergy clinic with RLQ pain, + rebound and fever
- Allergist orders STAT RAST panel
 - Peanut 0.53kU/L
- Diagnosed with “Allergic Appendicitis” and sends patient home with EpiPen and peanut avoidance...

Workup for Chronic Urticaria

- Verify it is urticaria, bx if necessary.
- Exclude or evaluate for physical urticarias
- Medication review (NSAIDs, etc)
- Review patient perception of triggers
 - Then test to exclude (skin prick test/RAST)
- Thorough review of symptoms
- Consider the following tests:
 - CBC, ESR, Thyroid studies, H. pylori, ASST, “therapeutic blood draw”

Interpreting Allergy Tests

- Called “RAST” by convention
- Technically a newer generation FELA
- Reports <0.10 → >100.0
- Several foods have positive predictive values
 - Peanut - >19 = 95% PPV

Specialized Testing

- Basophil Histamine Release testing is done
- Basophil Activation Tests
- Limited Clinical Utility
- Please do not order a RAST panel.....

Interpreting Allergy Tests

- Take a history
- If history not consistent with IgE mediated allergy (headache, fatigue, abdominal discomfort, brain fog, fibromyalgia, constipation, poor growth)
- DO NOT ORDER RAST!!
-
- 30 second allergy consult – “can you eat peanuts? Yes?, You aren’t allergic to peanuts. Nice to meet you....”

Negative tests

- 5% of food allergy has negative skin test and negative RAST.
- If good history, MUST do challenge to diagnose/exclude.
- Highly variable sensitivity of RAST vs SPT for foods vs environmental vs drugs

Atopic dermatitis and skin disease

The effectiveness of levocetirizine and desloratadine in up to 4 times conventional doses in difficult-to-treat urticaria

Maria Stawik, MD,* Todor A. Popov, MD, PhD,* Tanya Kollmarova, MD,* Corélie Larroche, MD,* Stefania Knera, PhD,* Tereza Popova, MD, PhD,* Diana E. Church, MD,* Yael Shalita, MD, PhD,* and Martin K. Church, PhD, DSc**

Bizarre Anaphylaxis #4

- Semen induced anaphylaxis
- Human Seminal Plasma Hypersensitivity
- “Burning Semen Syndrome”
- Weidinger, Stephan, Ring, J, Kohn, F M. IgE-mediated allergy against human seminal plasma. *Chemical Immunology & Allergy*. 88:128-38, 2005.

CU treatment until 2013

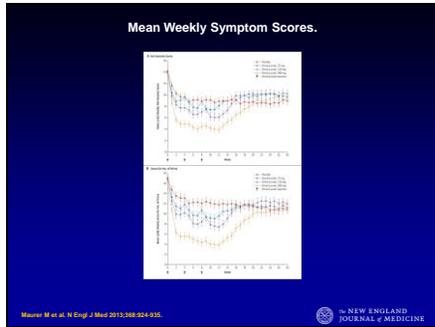
1. single or double dose of any nonsedating antihistamine
2. hydroxyzine 25mg qid → 50mg qid, can add H2 antagonist, LTMD
3. Steroids 10mg/d or 20-25mg qd, if higher doses needed, don't use.
4. Cyclosporine 200-300mg/d/ Cellcept
5. Methotrexate or IVIG for failures

Therapy



Omalizumab

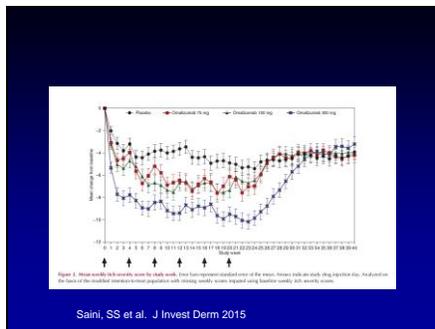
- Monoclonal anti-IgE – IgG
- Binds to the small amount of circulating free IgE
- IgE comes off mast cell to maintain equilibrium



Bizarre Anaphylaxis #5

Autoimmune progesterone dermatitis and its manifestation as anaphylaxis: a case report and literature review

Snyder, Joy L. Krishnaswamy, Guha. Autoimmune progesterone dermatitis and its manifestation as anaphylaxis: a case report and literature review. *Annals of Allergy, Asthma, & Immunology*. 90(5):469-77; 2003 May.



Angioedema

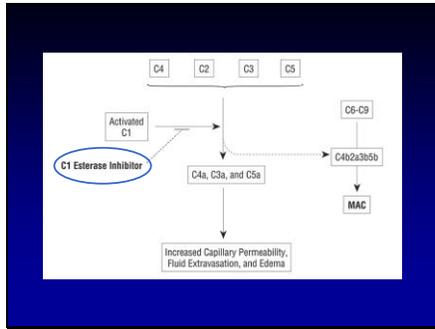
Results

- N= 20
- Significant improvement at 2 weeks, 16 weeks in all parameters (p ~0.003)
- Symptom free days at 16 weeks (p=0.0004)
- Basophils became “responders” by 4 weeks.
- All changes reverted back after omalizumab stopped.

• Abstract – Gober et al. *J Allergy Clin Immunol*. 2008;121(2):S147.

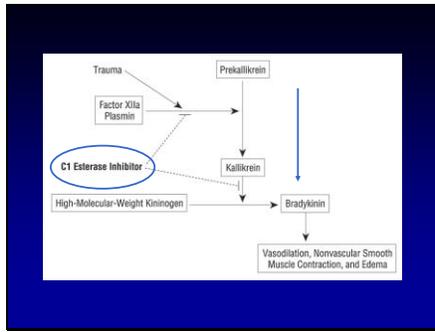
Angioedema

- Angioedema in the absence of Hives →
- Inherited Angioedema
- Acquired Angioedema
- Isolated Idiopathic Angioedema
- ACEI/ARB related Angioedema



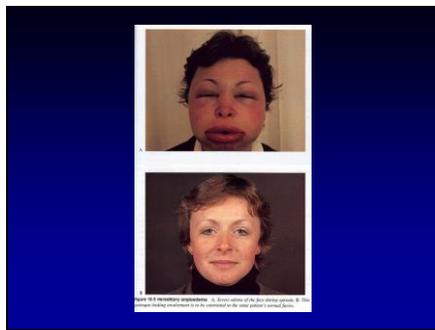
Hereditary Angioedema

- Edema of any part of body
- Recurrent abdominal pain (70-80%)
 - Uncommon in other causes of angioedema
 - 1/3 with HAE undergo needless surgery for abdominal attack
- Laryngeal involvement – occurs in 1/2



Hereditary Angioedema

- Autosomal Dominant
- Present in the first and second decade of life

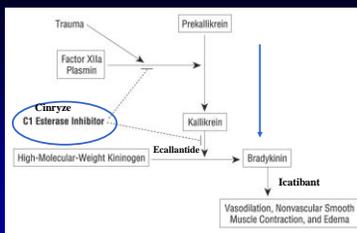


Hereditary Angioedema

- Type 1 – deficiency of C1 INH
 - Not necessarily a complement mediated phenomenon.
 - Related to C1 INH dependent bradykinin breakdown.
 - Will see Low C4, low C2 (during attack), and low C1 INH level (normal C1)

Therapy

- Acute – Steroids, Epi, antihistamines unlikely to have ANY effect.
 - Trach kit to bedside, supportive tx
 - FFP has a role, but in rare cases can worsen attack
 - C1 inhibitor
 - Ecallantide
 - Icatibant
- Danazol or Stanozolol – attenuated androgens which up regulate synthetic capability of hepatic cells.



Bizarre Anaphylaxis #6

