Chronic Urticaria

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Objectives

- Identify various external urticaria triggers
- Explained the various on label treatments for urticaria
- Recognize signs and symptoms suggestive of underlying, causative conditions associated with urticaria

Outline

- Urticaria Overview
- Histamine and Dermatographism
- Histology
- Autoimmunity
- Differential and Diagnostic Workup
- Treatment
- Prognosis

Question #1

- Of all cases of chronic hives, which of the following is the most commonly identified cause (not a trigger)?
  A. Cold weather
  B. Food allergy
  C. Co-workers
  D. Stress
  E. Unknown

Question #2

- Which of the following are considered “on-label” treatments for chronic hives?
  A. Prednisone
  B. Cetirizine (Zyrtec) and Omalizumab (anti-IgE)
  C. Cyclosporin
  D. Singulair
  E. None of the Above
**Question #3**

- All of the following are consistent with chronic idiopathic hives, except:
  - A. Intensely pruritic, raised lesions
  - B. Occasional swelling of the upper lip
  - C. Lesions last several hours, then disappear
  - D. Lesions appear without an identifiable trigger
  - E. Lesions last several days, leave behind ecchymoses and are associated with unintentional weight loss

**Urticaria – General Facts**

- Affects 25% of population, lifetime incidence
- Intensely pruritic “welts”
- Occur anywhere on the body
- Mast cell degranulation - histamine
- Lesion is circumscribed, raised and erythematous with central pallor
- Often associated with angioedema
- Can be presenting symptom in SLE, cryoglobulinemia, autoimmune thyroid disease, urticarial vasculitis etc.

**Urticaria – General Facts**

- Prevalence: about 0.5-5% of U.S. population
- Incidence: per year is about 1.4%
- Associated with angioedema in about 60% of cases
- Hives can be constantly present or episodically present
- Variable course, sometimes waxing and waning response to the same therapies

**Acute vs. Chronic Urticaria**

- **Acute**
  - < 6 weeks duration
  - Can be associated with identifiable cause (stinging insects, foods, drugs etc)
  - Think about drugs: B-lactams, salicylates, opiates, vancomycin, radiocontrast media, IV iron etc
  - Allergy testing can be useful
- **Chronic**
  - > 6 weeks (continuously or intermittently present)
  - Rarely associated with identifiable cause
  - Allergy testing rarely useful as the process involves direct mast cell irritation (not an allergic antibody mediator)

**CU – Secondary Causes**

- **Allergy**
  - Rarely, IgE-mediated reactions from foods, drugs, or other allergens
- **Infection**
  - Viral: hepatitis B and C, EBV, HSV, others
  - Helicobacter pylori infections
  - Helminthic parasitic infections
- **Systemic conditions**
  - Specific complement component deficiencies
  - Cryoglobulinemia (e.g. with hepatitis C and chronic lymphocytic leukemia)
  - Serum sickness
  - Connective tissue diseases (e.g. SLE, juvenile rheumatoid arthritis)
  - Thyroid disease (both hypothyroidism and hyperthyroidism)
  - Neoplasms (particularly lymphomatoid malignancy and lymphoproliferative disorders)
  - Other endocrine disorders (e.g. ovarian tumors), OC use
- **Autoantibody-associated urticaria**
  - Presence of autoantibodies
  - Thyroid autoantibodies
  - IgE receptor autoantibodies
Immune Cell Sources of Histamine

Dermatographism
- "Skin writing"
- Traumatically-induced urticaria
- When scratched, skin turns white (reflex vasoconstriction) followed by pruritus, erythema and swelling (hive)
- 2-5% of population, young adults
- No antigen identified, histamine is mediator
- Biopsy: edematous tissue, no increased cellularity
- Hives appear rapidly, gone within 1-2 hours

Urticaria Triggers
- Physical Triggers: (pressure, cold, heat, perspiration, solar, aquagenic, vibratory)
- Viral illnesses
- Drugs (antibiotics, NSAIDs...)
- Stress/anxiety
- Plant or animal exposure
- Travel or unusual setting (hotel, spa, vacation)
- Inhaled, irritant exposures
- Foods (strawberries, sulfites in wines, alcoholic beverages, others)
- Others as identified by the patient
- Cause vs. trigger commentary in patient care

Autoantibodies
- ~40% of patients with CU have autoantibodies, or chronic autoimmune urticaria (CAU)
- Most antibodies are IgG auto-antibody directed to the high-affinity IgE receptor (alpha subunit)
- Some are IgG auto-antibodies directed at IgE
- Autoantibodies shown by:
  - Autologous serum intradermal skin test, which demonstrates the triggering of cutaneous mast cells in the dermis by the autoantibody found in the patient’s serum
  - Basophil histamine release assay – aka the “Chronic Urticaria Index” test
CU - Histology

- Mixed cellular, perivascular infiltration
- The infiltration is mainly mononuclear cells
- Neutrophils and eosinophils present in both short and long duration wheals
- Mast cell counts can increase in upwards of 10-fold in the dermis
- Skin biopsy NOT normally required to make diagnosis of chronic urticaria

Urticarial Vasculitis

- Histopathology consistent with leukocytoclastic vasculitis, predominantly neutrophils
- Characterized by hives lasting >24hr, painful, burning lesions > pruritic, palpable purpura, residual hyperpigmentation
- Extracutaneous disease is common - associated with paraneoplastic syndromes, drug reactions, infections, autoimmune disorders...
- Look for increased ESR, complement consumption
- Relatively emergent steroid therapy often warranted
- Up to 5% of CU patients!!!!

<p>| Table 4 |</p>
<table>
<thead>
<tr>
<th>Histopathologic Features of Urticarial Vasculitis</th>
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<tbody>
<tr>
<td>Urticarial vasculitis</td>
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<tr>
<td>Leukocytes</td>
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<tr>
<td>Location</td>
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<tr>
<td>Endothelial cell swelling</td>
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<tr>
<td>Leukocytoclasia</td>
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<td>Red blood cell extravasation</td>
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Diagnostic Evaluation

- The diagnosis of chronic urticaria made almost solely on the basis of H&P
- Pursue laboratory investigations, ONLY IF CLINICAL SUSPICION EXISTS FOR A SECONDARY ETIOLOGY
- CBC, ESR, ANA, complement levels, thyroid auto-antibodies, hepatitis B surface antigen, hepatitis C Ab, SPEP
- One series* showed that 1 out of 356 cases (1,872 total lab tests) benefited from a "laboratory workup" for chronic urticaria
- Routine testing to foods and/or food additives NOT indicated
- Consider skin biopsy if urticarial vasculitis a concern


Therapy – Antihistamines – Mainstay for Relief of Pruritus

- First generation H1 receptor blockers:
  - H1 blockers are limited by sedation and anticholinergic side effects (dry mouth, diplopia, blurred vision, urinary retention, vaginal dryness)
  - Hydroxyzine 25-200mg, four times per day, scheduled
  - Cyproheptadine 2-4mg 3 times per day (esp. cold urticaria)
  - Doxepin 10-75 mg, taken 30 minutes before bedtime to prevent nocturnal itching, promote sleep
- Gradual up-titration can be useful

Stanaland 2002
Therapy – Antihistamines – Mainstay for Relief of Pruritus

- Second generation H1 receptor blockers:
  - Loratadine 10mg QD-BID
  - Cetirizine 10-40 mg per day
  - Fexofenadine 60-180mg BID
  - Levocetirizine 5mg QD-QID*
  - Desloratadine 5mg QD-QID*

- Advantages over first generation H1 blockers:
  - Less frequent dosing
  - Non- or low sedating

  * Staevska et al in J Allergy Clin Immunol 2010;125:676-82

Therapy – H2 Blockers

- Usually added to H1 blocker therapy
- Ranitidine 150mg BID, nizatidine 150mg BID, cimetidine up to 800mg BID, famotidine 40mg QD
- Cimetidine can increase levels of doxepin...

Therapy – Leukotriene Modifiers

- Besides histamine mediating the immediate urticarial response, a late phase reaction occurs
- Leukotrienes play a partial role in mediating this late phase reaction, especially in chronic forms of urticaria
- Others include PGD2, proteases, proteoglycans etc..
- Also used in treatment of asthma, rhinitis and atopic dermatitis
- Thought of as an add-on therapy to antihistamines and/or steroid sparing agents

  Erbagci 2002

Therapy – Thyroid Replacement

- Hashimoto’s disease is the only chronic condition with a common association to CIU and angioedema
- A handful of studies on thyroid replacement in euthyroid patients with thyroid antibodies, no consensus
- No tests (including thyroid antibodies) with predictive value regarding the value of thyroid replacement
- If hypothyroid, then replete thyroid hormone

Therapy - Steroids

- Effective, typically
- Can be used in extreme exacerbations with good control of symptoms
- Patients can be very reluctant to stop steroids due to tremendous efficacy
  - Lowest effective dose
  - Alternate day dosing
- Constant monitoring for SE’s and reassessment

Anti-IgE Therapy - Omalizumab

- Recombinant humanized mAb that binds to free IgE and inhibits binding of IgE to FcεRI, the high-affinity IgE receptor.
- Omalizumab reduces the number of FccRI receptors on the surfaces of mast cells and basophils
- Approved for poorly-controlled, persistent allergic asthma in 2003
- FDA-approved for anti-histamine resistant CIU in 2014
Omalizumab
- Dose and administration (hives):
  - 150-300 mg SC once every 4 weeks (not at home)
  - Even though it is an anti-IgE antibody, no baseline IgE level is needed prior to therapy
  - No available biomarkers to predict efficacy
  - Side effects include injection site redness and atypical anaphylaxis (black box warning)
  - Cost and access to omalizumab is an obstacle to therapy
  - Typically given in allergy or pulmonary offices, infusion centers, occasional some primary care as well

CU: What Do I Do?
- History and Physical
- Allergy testing + for reassurance
- If patient is antihistamine naïve:
  - Cetirizine 10 mg AM, 10 mg bedtime
  - Ranitidine 150 mg AM, 150 mg bedtime
  - Singular 10 mg bedtime
  - Trigger avoidance
  - Directed secondary workup
  - Follow up 2-4 weeks

CU: What do I do?
- If second generation antihistamines not working, then:
  - Short course (or 2) of oral steroids
    - Kenalog 80 mg IM or prednisone 30 mg per day for 5 days, then 10 mg for 5 days
    - Hydroxyzine 100 mg AM Noon PM Bedtime
    - Plaquenil 200 mg twice daily
    - Cyclosporin 100 mg once-twice daily
    - Sulfasalazine 500 mg daily-twice daily
    - Dapsone 50 mg daily
    - Colchicine 0.6 mg once-twice daily
    - Omalizumab

Unproven Therapies
- Steroid – sparing agents:
  - Dapsone – check for G6PD deficiency first given the association with hemolytic anemia
  - Cyclosporin – hypertension, hirsutism
  - Hydroxychloroquine – check G6PD level, periodic eye exams to evaluate for defects in accomodation or convergence, corneal deposits or retinal toxicity
  - Mycophenolate mofetil - immunosuppression
  - Sulfasalazine – rare agranulocytosis
  - Methotrexate – multiple, potential toxicities
  - Warfarin

Prognosis
- No indication thus far in literature that suggests that the natural history of CU is influenced by treatment modalities
- Symptom-based “treatment” only
- Prognosis (+/- treatment) summed up as follows (from a review of several authors reporting a course for CU):
  - 50% will resolve within 6 months
  - 20% will resolve within 36 months
  - <2% will resolve within 25 YEARS
- Caveat: ~50% will experience at LEAST one recurrence of CU after apparent spontaneous resolution

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Stanaland 2002
Ruddy 2001
Baltrani 2002
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Urticaria Summary
- “Twitchy/leaky mast cell” syndrome, histamine is main mediator
- 90+% of all chronic urticaria is either autoimmune or idiopathic
- Urticaria as a herald of underlying and consequential systemic disease process
- Foods/food additives are NOT causative (but can serve as triggers) as a rule
- Essentially unknown and unalterable course with present – day therapies

Thank You!