Serum Sickness

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History

- 1st described in 1905, as human rxn to equine diphtheria antitoxin (von Pirquet and Shick)
- 8-13 days later: rash, fever, +/- facial edema, arthralgia, local LAD, albuminuria
- Later, similar seen w/ other horse antitoxins, antivenins
- Soon recognized with NSAIDs, PCN
- Now w/ monoclonals, antithymocyte glob
Definition

- Immune complex (type III) hypersensitivity reaction
- Rash
  - Urticarial, morbilliform, or angioedema
- Arthralgia or Arthritis
- Fever
- Onset 5-14 days (may be up to 21) after drug or foreign protein exposure (does not require prior sensitization)
- May occur 1-3 days later if previous exposure
Epidemiology

- Decreasing incidence in U.S. due to:
  - ↑ in vaccines --> ↓ need for antitoxins & more refined antitoxins (rabies, tetanus)
- Adult cases: antitoxin/-sera usually responsible
  - 50-85% incidence in recent antithymocyte trial
  - RCT of mouse Mab to TNFα: 2.3% incidence
- In children, more often ATBX-associated:
  - cefaclor >> TMP-SMX > cephalexin > amoxicillin
  - Avg incidence 2/100K to 1/10 million
- Sx are dose- and antigen type-dependent:
  - Animal source >>> drugs in terms of risk
  - Immunogenicity of rabies (16%) > tetanus (3-5%)
Etiology - 1

- Historically, antitoxins & antivenins
  - tetanus, botulinum, rabies, snakebites
- Now often due to immunogenic haptens
  (often difficult to prove causality)
- Infections with circulating immune complexes
  - HBV, HCV, endocarditis/bacteremia, ?HIV
- Insect stings: bees, mosquitoes, ticks
- PAbs/MAbs from horse/rabbit/mouse serum:
  - Antithymocyte globulin, OKT3
Meds

ATBX: PCNs, cephalosporins, sulfonamides, cipro, tet, metronidazole, rifampin, streptomycin, griseofulvin

Anticonvulsants: phenytoin, carbamazepine

Psychotropics: buproprion, fluoxetine, barbiturates

AntiHTN: propranolol, captopril, hydralazine, CH4dopa

Antidysrhythmics: procainamide, quinidine

Anticancer: mercaptopurine

Antiinflammatories: gold, penicillamine, NSAIDs

Other: allopurinol, iodides, methimazole, streptokinase
# Hypersensitivity Rxns

| I          | IgE → mast cells, basophils  
|            | → histamine/LT’s  
|            | → edema, bronchospasm | Local/Atopy (eczema, allergies, asthma)  
|            |                     | or  
|            |                     | Systemic (anaphylaxis)  
| II         | IgG, IgM → complement/phago/NK  
|            | → cytotoxic immune response | Txfusion rxn, ITP, Goodpasture’s  
|            |                     | (+/- Graves’, myasthenia)  
| III        | IgG, IgM (IgA) → immune complexes | Poststrep GN, serum sickness, PAN, SLE  
|            |                     | Hypersensitivity pneumonitis  
|            |                     | Many more w/ complexes demonstrated  
| IV         | No Abs: sensitized T cells | Chronic transplant rejection  
|            |                     | Contact dermatitis, Hashimoto’s  
|            |                     | Mycobacterial & fungal infex |
Pathophysiology

- Immune complex process (Type III hypersensitivity)
- Type of Ag influences Ig type, influencing pathology
  - Typically IgG
  - Occasionally IgM, but more effectively cleared by RES
  - Rarely IgA
- Deposition of immune complexes in vessel walls, joints, and renal glomeruli
- Activate complement pathway --> vascular wall injury
  --> PMN influx --> inflammation w/ tissue injury
Histopathology

Inflammation of small vessel endothelium

Skin > renal, GI, joints > CNS

- Leukocytoclastic vasculitis
  - Neutrophilic (<24 hrs old) or mononuclear infiltration of vessel wall & perivascular region
  - Most prominent in postcapillary venules
  - Renal IgG + C3a + C5a deposits along GBM
  - Mononuclear infiltration of synovium

- Little correlation between Sx and histologic pattern
- Complexes can be detected: C1q or Raji cell assay
Common Presentations

- Rash (95%): pruritic, URTICARIAL, morbilliform, scarlatiniform, or angioedema
  - May start with pruritus & erythema @ injection site
- Fever (~all) (usu <40°C) (precedes rash in 20%)
- Arthralgias (30-60%)
- Myalgias & Headache (40-60%)
- Arthritis (10-50%) (knee, ankle, MCP, wrist) (symmetric)
- Regional lymphadenopathy (20%)
- Facial edema (d/t albuminuria and/or rash)
- Duration: 7-30 days, Onset 5-21 days post exp
Up to 50% present with

- **Visceral target organ involvement**
  - Rare, but may be severe -- may include:
    - Renal (glomerulonephritis, acute failure)
    - Lymph (generalized LAD, splenomegaly)
    - Neuro (CN palsy, peripheral/brachial/optic neuritis, GBS, myelitis, encephalitis)
    - Cardiac (pericarditis, myocarditis)
    - Pulmonary (pleuritis)
    - GI (terminal ileitis)
Diagnosis

- History: offending drug or infection
- Skin biopsy: leukocytoclastic vasculitis of venules/cap’s
- Leukopenia or slight -cytosis +/- plasma cells, +/- eo’s
- Low C3, C4 levels (more with heterologous serum than with drug-induced serum sickness)
- Elevated ESR
- Polyclonal gammopathy, transient IgG spike
- Mild proteinuria, micro hematuria, hyaline casts
- +/- cryoglobulins, often mixed IgG-IgM type
  - (may indicate mixed cryoglobulinemia due to chronic hepatitis C infection)
Differential diagnosis

- Cryoglobulinemia
- Immediate hypersensitivity reaction
- Mononucleosis
- Viral hepatitis
- Urticarial vasculitis with hypocomplementemia
- SLE
- Infectious endocarditis
- Acute rheumatic fever
- Poststreptococcal glomerulonephritis
Treatment

- Discontinue offending agent
- Recognize causative infection and treat
- Consider rheum/immunol eval
- NSAIDS, antihistamines for Sx relief
- Steroids if signific, if multisystem Sx, or if agent needs to be continued
  - Review (n=95): 54 no Rx, 26 NSAIDs, 14 steroids
  - At 16 months, 93/95 full recovery, 2 mild renal CRI
- Rarely: colchicine, dapsone, pentoxifylline
Prognosis

- Typically excellent
- Exceptions: progressive GN, CNS injury
- Reconsider Dx if Sx persist > 3-4 weeks
- Avoid future exposures to agent
References