Introduction

- Historically, the term serum sickness connotes a self-limited immune complex disease caused by exposure to foreign proteins or haptens. Immune complex formation is a common event and does not typically cause symptoms. However, an immune reaction can occur, as in the case of serum sickness.
- Von Pirquet and Shick first described the syndrome in 1905, describing fever, skin eruptions (mainly consisting of urticaria), joint pain, and lymphadenopathy in regions draining the site of injection after patients were given antitoxin in the form of horse serum. Later, physicians reported a similar clinical picture after the injection of other equine-based antitoxins and antivenoms. Certain medications (eg, penicillin, nonsteroidal anti-inflammatory drugs [NSAIDs]) have also been associated with serum sickness–like disease.
- Identifying serum sickness was a landmark observation in understanding immune complex diseases.

Causes

- Currently, the most common cause of serum sickness is hypersensitivity reaction to drugs.
  - Proteins of other species, such as antitoxins, antivenins, hormones from other species, and streptokinase
  - Antibiotics and other antimicrobials, such as cephalosporins, ciprofloxacin, griseofulvin, lincomycin, metronidazole, penicillins, streptomycin, sulfonamides, and tetracyclines
  - Other drugs, such as allopurinol, barbiturates, carbamazepine, fluoxetine, hydantoins, indomethacin, iron dextran, methimazole, phenylbutazone, procarbazine, propranolol, and thioracil
- Polyclonal and monoclonal antibodies prepared from horse, rabbit, or mouse serum (eg, antithymocyte globulin, OKT-3) have also been found to cause serum sickness.
- Omalizumab, a monoclonal antibody used to treat allergy-related asthma, has recently been reported to cause serum sickness–like syndrome.
- Various different case studies (20 cases in the literature as of August 2007) have linked serum sickness–like syndromes to rituximab therapy used to treat various diseases, including autoimmune diseases, mixed cryoglobulinemia, and lymphoma.
- Stings from insects in the order Hymenoptera (eg, bees, mosquitoes) and tick bites may cause serum sickness.
- Infectious diseases involving circulating immune complexes (eg, hepatitis B, infectious endocarditis) may cause serum sickness–like reactions. These conditions are often associated with circulating cryoglobulins.

Pathophysiology

- Serum sickness is an example of the type III, or immune complex–mediated, hypersensitivity disease. The molecular size, charge, structure, amount, and valence of the antigen involved influence the type of immune complexes formed.
- After the initial exposure to a foreign antigen in the absence of a preexisting antibody, serum sickness can develop within 1-2 weeks. Upon subsequent exposure, however, serum sickness develops sooner. The disease appears as the antibody formation begins, and the pathogenesis of serum sickness is related to protracted interaction between antigen and antibody in the circulation, with antigen-antibody complex formation in an environment of antigen excess.
- The immunological interactions observed in serum sickness occur when antigens capable of remaining in the circulation for long periods incite antibody formation. Typically, serum protein molecules are removed from the circulation by nonimmune processes that are not yet completely understood. Small complexes
usually circulate without triggering inflammation, and large complexes are cleared by the reticuloendothelial system. However, intermediate-sized complexes that develop in the context of slight antigen excess may deposit in blood vessel walls and tissues, where they induce vascular and tissue damage resulting from activation of complement and granulocytes.

- Endothelial cells increase the expression of adhesion molecules, and proinflammatory cytokines are released by monocytes and macrophages. Subsequently, addition inflammatory cells are recruited, and necrosis of the small vessels develops. Complement activation promotes chemotaxis and adherence of neutrophils to the site of immune complex deposition. This may be facilitated by increased vascular permeability due to release of vasoactive amines from tissue mast cells. At this point, complement levels fall to half their levels prior to the antibody response.3 This clinicopathological syndrome usually develops within 1-2 weeks of antigen injection.

- Free antigen continues to clear from the blood, leading to antibody excess and the formation of large immune complexes, which are quickly removed by circulating macrophages. Finally, the antigen is no longer detectable, and the level of circulating antibodies continues to rise. Clinical recovery is usually apparent after 7-28 days, as intermediate-sized immune complexes are cleared by the reticuloendothelial system.

- Secondary serum sickness is the result of antigen recognition by presensitized cells of the immune system and is characterized by a shorter latent period, exaggerated symptoms, and a brief clinical course.

- Why immune complex disease occurs under certain circumstances is not known. Possible factors may include high levels of immune complexes and a relative deficiency of some complement components leading to a decreased ability to eliminate immune complexes.

**Age**

- In one study, serum sickness was more common in patients older than 15 years who were given antirabies serum. Antibiotic-associated serum sickness–like disease, however, is more frequently described in children younger than 5 years.

**Clinical features**

- Serum sickness develops 1-3 weeks after administration of the causative agent (in many cases a medication) is initiated but can occur within 12-36 hours in individuals who have been previously sensitized through an antecedent exposure.

- Symptoms described in serum sickness include the following:
  - Fever/malaise - 100%
  - Cutaneous eruptions - 93%
  - Arthralgias - 77%
  - Gastrointestinal complaints - 67%
  - Headaches - 57%
  - Myalgias - 37%
  - Blurred vision - 37%
  - Dyspnea/wheezing - 20%
  - Lymphadenopathy - 17%

- Specific GI symptoms may include abdominal pain, nausea, vomiting, or diarrhea.

- Chest pain or breathlessness due to pleuritis, pericarditis, or myocarditis is possible but rare.

- Fever: This develops in almost all patients with serum sickness, preceding skin rash in 20% of cases. The fever is characterized by high spikes that normalize within the same day.
• Skin symptoms
  o Rash (92% are urticarial): Most rashes associated with serum sickness are urticarial and/or serpiginous. They typically start on the anterior lower trunk or the periumbilical or axillary regions and spread to the back, upper trunk, and extremities.
  o Morbilliform or scarlatiniform rash, palpable purpura, erythema simplex or multiforme (less common)
  o Possible pruritus and erythema at injection site
• Arthritis (10%-50%), usually in the metacarpophalangeal and knee joints and usually symmetrical
• Edema, which can be limited to site of injection but can also be observed in the face
• Regional lymphadenopathy
• Carditis
• Acute renal failure (rare), proteinuria, hemoglobinuria
• Neurologic complications
  o Peripheral neuritis
  o Brachial plexus neuritis
  o Optic neuritis
  o Cranial nerves palsies
  o Guillain-Barré syndrome
  o Myelitis
  o Encephalitis (rare)

Mortality/Morbidity

• Although occasional reports show mortality resulting from progressive glomerulonephritis or severe neurological complications, serum sickness is usually self-limited, and recovery is the rule.

Clinical investigations

• Patients with serum sickness may have leukopenia or mild leukocytosis, with or without eosinophilia. Plasma cells may be observed on a peripheral blood smear.
• The erythrocyte sedimentation rate is usually elevated.
• Patients may have polyclonal gammopathy or a transient monoclonal immunoglobulin G (IgG) spike.
• Urinalysis may reveal mild proteinuria or hematuria, and serum creatinine levels may be transiently elevated.
• Complement levels (C3, C4) are often decreased.
• Cryoglobulins, often of the mixed (IgM-IgG) type, may be present.

Treatment

Medical Care

• Withdrawal of the offending agent is the mainstay of treatment in serum sickness. Anti-inflammatories and antihistamines provide symptomatic relief. Severe cases (multisystem involvement with significant symptomatology) may warrant a brief course of corticosteroids.
• In some cases, plasmapheresis can attenuate serum sickness.
Medication

- The goals of pharmacotherapy are to reduce morbidity and to prevent complications.
- Nonsteroidal anti-inflammatory drugs
- These agents have analgesic, anti-inflammatory, and antipyretic activities. Their mechanism of action is not known, but they may inhibit cyclooxygenase activity and prostaglandin synthesis. Other mechanisms may also exist, such as inhibition of leukotriene synthesis, lysosomal enzyme release, lipoxygenase activity, neutrophil aggregation, and various cell-membrane functions

Ibuprofen (Motrin, Ibuprin)

- Decreases inflammation by blocking prostaglandin synthesis and reduces fever by acting on the hypothalamic temperature-regulating center. Usually administered for mild symptoms of arthralgia, myalgia, or fever.
- Dosing
  - Adult: 200-800 mg PO qid; not to exceed 3200 mg
  - Pediatric: <12 years: 5-10 mg/kg PO qid, >12 years: Administer as in adults

Diphenhydramine HCL (Benadryl)

- Blocks histamine H1 receptors on the target tissue. For urticarial rash.
- Dosing
  - Adult: 25-50 mg PO/IM qid
  - Pediatric: 5 mg/kg/d PO/IV/I M divided tid/qid

Prednisone (Deltasone, Orasone, Sterapred)

- Acts by altering the number and availability of leukocytes, reducing vascular permeability, and suppressing cytokines. Mainstays of treatment in severe cases; usually administered in moderate doses for 1-2 weeks. This or other oral forms of corticosteroids (eg, prednisolone) are useful in managing mild-to-moderate serum sickness treated in an outpatient setting.
- Dosing
  - Adult: 20-40 mg/d PO qd or divided bid/qid; taper over 2 wk as symptoms resolve
  - Pediatric: 0.2-0.5 mg/kg/d PO qd or divided bid/qid; taper over 2 wk as symptoms resolve

Differential Diagnoses

- Cryoglobulinemia
- Kawasaki Disease
- Glomerulonephritis, Poststreptococcal
- Leukocytoclastic Vasculitis
- Hepatitis, Viral
- Sickle Cell Anemia
- Hypersensitivity Reactions, Immediate
- Systemic Lupus Erythematosus
- Infectious Mononucleosis
- Infective Endocarditis