Serum Sickness

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Case Overview

History of Presenting Illness
A 5-year-old male arrives at the emergency department (ED) with his mother who is concerned her son is having an allergic reaction. She reported that the week prior, he presented to his family doctor's office with general malaise and productive cough. He tested positive for Group A Streptococcal infection and was started on amoxicillin. The day prior to arriving at the ED, he developed a purpuric urticarial rash that covered his trunk and extremities which continued to progress. He complained of bilateral ankle pain and fatigue. The patient had no past medical history, was not on any other medications, his family history was unremarkable, and had no known allergies. There was no recent change in diet or environmental exposures.

Physical Exam
The patient had a temperature of 38.3 degrees. All other vital signs were normal. On exam, his gait was antalgic. His trunk and extremities had multiple large, erythematous, annular plaques. The lesions were pruritic, non-blistering, and non-photo sensitive (see Figure 1). His lips were erythematous, and cheeks appeared flush. His mucous membranes were spared. Head and neck exam was otherwise unremarkable. His ankles were swollen bilaterally, limited range of motion in all directions and non-tender to palpation. His knees were also swollen bilaterally, non-tender, positive patellar tap test. Wrist did not show signs of swelling, restricted motion, or pain.

Investigations
Based on the wheal-like rash, Lyme disease, Vasculitis and Kawasaki were ruled out. Reactive arthritis was unlikely with a lack of family history. Throat swab was collected to rule out post-streptococcal glomerulonephritis. Based on the age of the child, further blood work was held while throat swab was analyzed as to not cause distress. Renal function, CPR and Lyme anti-bodies may be indicated if the child was otherwise unwell with high degree of suspicious of a more severe diagnosis.

Diagnosis
Given the presentation, you consider serum sickness-like reaction as a diagnosis. You consult dermatology for their opinion.

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The dermatologist on call confirms the diagnosis as serum sickness-like reaction.

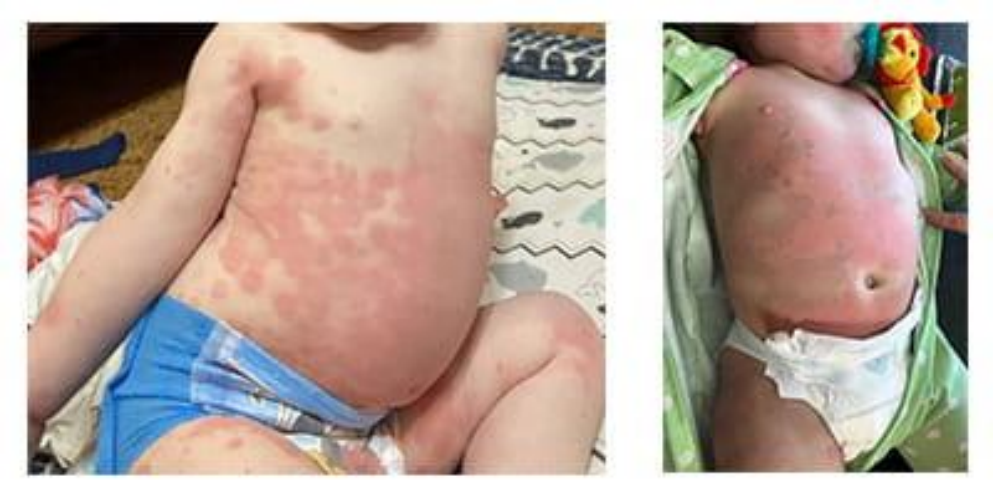

Figure 1. Drug-induced urticaria in a pediatric patient (CincinattiChildren's.org).

Serum Sickness-Like Reaction

Serum sickness was originally named due to the compilation of symptoms following injection of horse serum for treatment of scarlet fever and diphtheria[1]. Traditionally, the term serum sickness should be reserved for those reactions following a heterologous or chimeric protein therapeutic.

Other, similar acute inflammatory presentations are referred to as serum sickness-like reactions (SSLR), and classically present with a characteristic rash, fever, malaise, and polyarthralgia or polyarthritis one to two weeks after exposure to a causative agent[2]. If a patient has previously been exposed to the causative agent, the reaction may occur sooner. Serum sickness-like reaction is a type of hypersensitivity reaction following the administration of a substance, including vaccines or other medicines. Common antibiotics shown to result in SSLR are cefaclor, amoxicillin, and trimethoprim-sulfamethoxazole[3-5]. Serum sickness-like reaction is also highly associated with certain non-steroidal anti-inflammatory drugs, anti-cancer agents, and biologics[4]. Serum sickness-like reaction can also occur following certain infections, particularly streptococcal infection, and hepatitis B[6,7].

Normally self-limiting, SSLR most often subsides within weeks after discontinuing the responsible agent[8]. Onset of symptoms of SSLR is tri-phasic, with the first peak at day 5 post exposure, second peak at day 7 and third at day 10[10]. Although most seen in adults, SSRL are an increasingly common etiology of acute arthritis in children[9,10].

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The **differential diagnosis** for such reactions can include, but is not limited to:

- Autoimmune diseases, including systemic lupus erythematosus, reactive arthritis.
- Drug reactions, such as drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome, drug-induced sweet syndrome.
- Infectious diseases, including Epstein-Barr virus, Lyme disease, erythema multiforme, disseminated meningococcemia.
- Vasculitis, including IgA vasculitis (Henoch-Schoenlein purpura), hypersensitivity vasculitis.

Diagnosis

The **diagnosis** of SSLR is typically based on the characteristic compilation of symptoms, including the typical urticarial-like lesions, arthralgias, with or without fever, secondary to, most commonly, drug exposure[11]. It's important to rule out Steven-Johnson Syndrome/Toxic Epidermal Necrolysis in both pediatric and adult populations with lack of mucous membrane involvement[8].

Pathophysiology

Serum sickness-like reaction is a Coombs type III/immune complex mediated hypersensitivity reaction. The formation of antigen-antibodies complexes, involving an antigen and coinciding antibody, are required for the reaction to occur. The immune complex formation of serum sickness is mediated by C3 and C5a complement proteins which recruit mast cells and neutrophils to release histamines resulting in vascular permeability (Figure 2). Normally excreted by phagocytes, they are unable to clear these complexes due to the overwhelming number of complexes formed or the under performance of the mononuclear phagocyte system. These immune complexes target certain organs in the body—why they target some and not others are not well understood. Typically, they will target joint spaces, presumed to be due to the fenestrations into the synovial fluid. Once deposited in areas of the body, these complexes will activate an inflammatory response[12].

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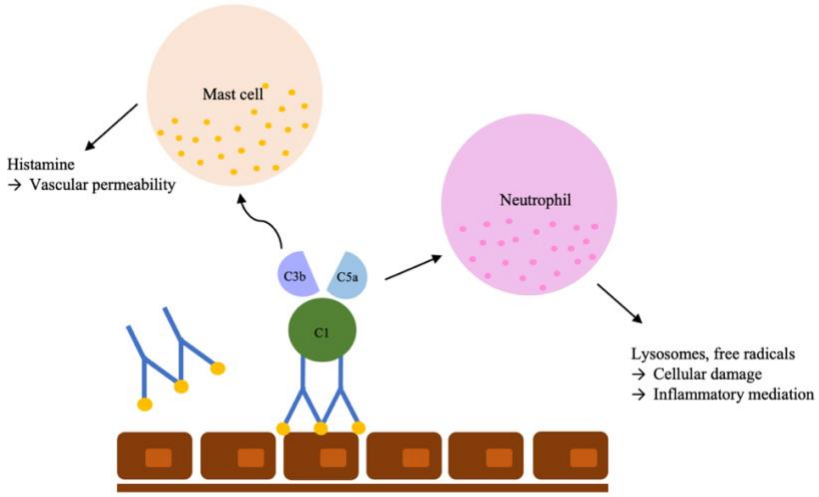

Figure 2. Type III immune complex mediated hypersensitivity mechanism of serum sickness.

Treatment

Serum sickness-like reactions resolve when the agent responsible is discontinued and cleared from the patient's system. Most patients do not require additional treatment. Symptoms typically subside within two to three weeks, but in some cases may linger for up to three months. If required, arthralgias and fever can be treated with non-steroidal anti-inflammatory and analgesic medications[11]. For patients with severe symptoms, glucocorticoid medications can be prescribed. Intravenous immunoglobulin may be indicated for worsening or unresolving symptoms. Outcomes of serum sickness and SSLR are good, and prolongation of symptoms more than 40 days is uncommon[10]. Offending drug should be avoided in the future. In situations where the causative agent cannot be discontinued, treatment is highly dependent on the drug in question, and should be based on a case-by-case basis[13].

Case Conclusion

While in the ED, the dermatologist on call recommended to discontinue the amoxicillin that the patient was taking for Group A Strep. Supportive measures were also recommended, as well as analgesics or NSAIDs for symptom management. The dermatologist agreed to follow up with this patient in the subsequent days to ensure resolution of symptoms and whether future treatment was needed.

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