Clinical Pharmacology & Toxicology Pearl of the Week

~ Serum Sickness ~

Introduction:
Serum sickness is an immune-complex-mediated hypersensitivity reaction, typically classified as a type III hypersensitivity reaction. This condition is most associated with exposure to foreign antigens such as therapeutic serum, monoclonal antibodies, or certain medications.

Pathophysiology:
- Serum sickness involves the formation of immune complexes between circulating antigens and host antibodies (IgM, IgG, IgE, IgA).
- These immune complexes deposit in small blood vessels, triggering the activation of the complement system (C3a is a potent anaphylatoxin, and C5a is a chemoattractant) and recruitment of inflammatory cells.
- This results in tissue damage and the characteristic clinical manifestations.
- The reaction typically occurs 7-14 days after antigen exposure, correlating with the time required for antibody production.

Etiology:
Serum sickness is a dose-dependent reaction: Higher doses of the administered agent are more likely than lower doses to result in serum sickness. It also can develop after a patient's initial exposure to a drug or after subsequent exposures. Common causative agents are heterologous proteins or antigens, which can include:
- Antiserum treatments (e.g., anti-venom or anti-toxin therapy).
- Monoclonal antibodies (e.g., rituximab, infliximab).
- Certain medications, such as penicillin, cefaclor, or sulfonamides.
- Vaccines containing animal-derived proteins.

Clinical Presentation:
The onset of serum sickness typically occurs within 1-2 weeks after exposure to the antigen, which is intermediate compared to the immediate onset of type I reactions (minutes) and the delayed onset of type IV reactions (>2 weeks). If the patient still has IgG or IgE antibodies resulting from a previous exposure when that drug or serum is given again, an immediate reaction (such as an acute anaphylactic reaction) may occur, giving rise to a mixed clinical picture that has features of both anaphylaxis and serum sickness.

Common symptoms and diagnostic criteria for serum sickness include the classic triad of fever, rash, and arthralgia. Additional symptoms can include lymphadenopathy, albuminuria, and nephritis.

- Fever: This is often one of the earliest symptoms, accompanied by chills and malaise.
- Rash: Typically, the rash is urticarial or morbilliform and can be widespread. It may also present as purpura or erythema multiforme.
- Arthralgia: Joint pain is common and can affect multiple joints, often symmetrically. It may be accompanied by swelling and tenderness.
- Lymphadenopathy: Swollen lymph nodes are frequently observed, particularly in the cervical region.
- Albuminuria and Nephritis: Proteinuria and hematuria indicate renal involvement, ranging from mild to severe nephritis.
- Gastrointestinal symptoms: Nausea, vomiting, and abdominal pain in some cases.

Differential Diagnosis:
The differential diagnosis for serum sickness includes:

- Viral exanthems (e.g., Epstein-Barr virus or cytomegalovirus infection)
- Systemic lupus erythematosus (SLE)
- Hypersensitivity and urticarial vasculitis
- Rheumatic fever
- Scarlet Fever
- Lyme disease
- Reactive arthritis
- Disseminated gonococcal disease
- DRESS
- Hypersensitivity reactions (e.g., type I or IV hypersensitivity)

Diagnostic Workup:
The diagnosis of serum sickness is primarily clinical, supported by a history of recent antigen exposure and characteristic symptoms. Laboratory findings may include:

- Elevated inflammatory markers (e.g., ESR, CRP).
- Leukocytosis with eosinophilia.
- Urinalysis may reveal hematuria and proteinuria.
- Increased levels of circulating immune complexes (IgG and IgM)
- Low complement levels (C3, C4).
- Evidence of immune complexes (e.g., positive rheumatoid factor or cryoglobulins).
- Histology will show leukocytoclastic vasculitis, which is indicative of immune complex deposition in small vessels. This is distinct from the histopathological findings in other types of hypersensitivity reactions.

Management:
Treatment of serum sickness focuses on supportive care, removal of the offending agent and symptomatic relief:

- Nonsteroidal anti-inflammatory drugs (NSAIDs) for fever and arthralgia.
- Antihistamines for pruritus and rash.
- Corticosteroids (e.g., prednisone) in severe cases such as higher fever (e.g., temperature >38.5°C [>101.3°F]), more severe arthritis and arthralgia, or more extensive rashes, including extensive vasculitis eruptions or when symptoms do not respond to initial measures.
- Severe cases may require more intensive immunosuppressive therapy.

Prognosis:
The illness is self-limited, and prognosis is excellent once the responsible drug is identified and removed. Symptoms resolved within days to weeks after cessation of the offending agent. Long-term complications are rare but may include persistent joint symptoms or renal involvement.

References:

1. Rituximab-Induced Serum Sickness: A Systematic Review. Karmacharya P, Poudel DR, Pathak R, et al.
2. Serum Sickness Induced by Alemtuzumab In a kidney-Pancreas Transplant Recipient. Yango A, Fischbach B, Bista B, et al.
3. Commentary. Al-Araji S, Ciccarelli O.
4. Childhood Serum Sickness: A Case Report. Chao YK, Shyur SD, Wu CY, Wang CY.
5. Transfusion-Induced Serum Sickness. Saegeman V, Wynendaele W, Kerre S, et al.
6. Severe Serum Sickness Reaction to Oral and Intramuscular Penicillin. Clark BM, Kotti GH, Shah AD, Conger NG.

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm, excluding stat holidays. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral, Specialist Link, and RAAPID. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.

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