CLINICAL VIGNETTE

Serum Sickness-Like Reaction in a Patient with Epstein Barr Virus and Amoxicillin Exposure

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Background

Serum sickness was first described in 1905 by von Pirquet and Schick in patients who had received horse serum as an antitoxin for the treatment of diphtheria and scarlet fever.[1] Serum sickness-like reaction (SSLR) classically presents with rash, fever, skin edema, and polyarthralgia or polyarthritis and is less severe in presentation than classic serum sickness. Symptoms usually begin 6 to 21 days after exposure to the inciting agent but may appear as early as 2 to 4 days after exposure.[2] Although the patient may appear very ill during the acute period, SSLR has a benign clinical course and resolves in a few days, but rarely lasts as long as several weeks.[3]

Case Report

A nine-year-old, previously healthy boy presented to the emergency department with an eight-day history of fever and new onset rash and vomiting. The patient initially presented three days prior to his pediatrician with a five-day history of fever and sore throat. With positive testing for streptococcal antigen in the clinic, the patient was diagnosed with streptococcal pharyngitis and started on amoxicillin. After three days of amoxicillin treatment, the patient developed a blotchy rash that was first noted behind the ears and rapidly spread throughout the body within a few hours on the day prior to admission. On the day of presentation to the emergency department, the patient was febrile to 103 F, had facial edema, severe pruritus, and one episode of non-bloody non-bilious emesis.

On examination, the patient was visibly uncomfortable and tachycardic to 137 beats/min. Physical exam was notable for bilateral conjunctival injection with limbic sparing, palatal petechiae, dry lips, cervical lymphadenopathy, edema of the hands and feet, swelling of the knees, a coalescent papular rash affecting the knees and a diffuse morbilliform eruption.

Initial laboratory testing demonstrated an elevated c-reactive protein, mildly elevated erythrocyte sedimentation rate, a positive rapid mononuclear spot test, and negative anti-streptolysin O antibody. EBV DNA PCR and EBV IgM antibody were slightly elevated, which was suggestive of an acute EBV infection. The white blood cell count was 11,000 cells/μL with a differential of 60% neutrophils, 32% lymphocytes, 5% monocytes, and 3% eosinophils. Other laboratory tests, including liver function tests, were within normal limits. The differential diagnosis included immunologic causes such as drug reaction with eosinophilia and systemic signs (DRESS), late-onset Stevens-Johnson syndrome, and polyarticular vs. systemic juvenile idiopathic arthritis (JIA). Other diagnoses such as vasculitidies including incomplete Kawasaki Disease or infectious etiologies such as group A streptococcus bacteremia, rheumatic fever, measles, coccidioides, rickettsia, parvovirus, and toxoplasmosis were considered.

Minor laboratory criteria for incomplete Kawasaki Disease were not met. Over the next two days, the rash began to slowly improve and the patient developed loose, watery stools and abdominal pain. Stool testing for C. difficile toxin was negative. An abdominal ultrasound was obtained to rule out EBV-related gastrointestinal complications such as acalculous cholecystitis and was within normal limits. Abdominal pain and loose stools were thought to be secondary to non-specific EBV colitis. Swelling in the hands and feet and pain in the bilateral wrists and ankles worsened. Given the constellation and progression of symptoms the final diagnosis was determined to be serum sickness-like reaction with a concurrent EBV infection. The patient was started on a five-day course of steroids and antihistamines and returned to baseline by day 14 of illness.

Discussion

Clinical presentation of SSLR often includes symptoms of rash, arthralgias, and lymphadenopathy. Fever may or may not be present and is typically low-grade when present.[4] Rash is often morbilliform or urticarial. Skin lesions often begin in the flexures and become generalized, eventually spreading predominantly to the trunk and lower legs. The rash often lasts greater than 24 hours. Other findings with SSLR, although rare, include erythema and edema of the hands and feet, gastrointestinal disturbances, palpable purpura (vasculitis), and facial swelling.

SSLRs are seen following drug exposures as well as viral infections. Cefaclor, a second-generation cephalosporin is the drug most commonly cited in the literature as leading to SSLR. Cefaclor-induced SSLR has been estimated at 0.024-0.2% per course of cefaclor prescribed.[5] Other drugs commonly implicated in the development of SSLR include amoxicillin, cephalexin, and trimethoprim-sulfamethoxazole. Four percent of reports of serum sickness were attributed to amoxicillin, 25% to cefaclor, 2% to cephalexin, and 2% to TMP-SMZ.[6] The most commonly reported infectious conditions leading to SSLR include streptococcal infections and viral infections including measles, rubella, parvovirus B19, non-polio enteroviruses, adenovirus, HHV6, and hepatitis B.[7] Vaccines have been associated with SSLR, most commonly the rabies vaccine, but also influenza, tetanus, and pneumococcal vaccines.[8] Unlike classic serum sickness, data indicates that high titers of antibodies and circulating immune complexes may not be responsible for the SSLR. However, there have been a few reports of circulating immune complexes in the sera of patients with SSLR most often with penicillin.[9]

Recommended laboratory tests when evaluating a patient with SSLR include CBC with differential, which may show eosinophilia and a reactive lymphocytosis. Inflammatory markers, including ESR and CRP, will be elevated. Urinalysis and serum chemistries may be helpful to differentiate classic serum sickness from SSLR. In classic serum sickness, proteinuria and transient mild hematuria is seen in 50% of patients as well as an occasional doubling of serum creatinine.[10] Infectious testing should be pursued based on clinical suspicion.

Ultimately, SSLR is a clinical diagnosis and an inciting agent is often hard to identify and isolate. The diagnosis is considered in patients presenting with an expansive dermatologic spectrum of rash with accompanying symptoms of fever and arthralgia/ arthritis.[3]

The first step in treatment includes discontinuation of the inciting agent and in cases of mild SSLR, symptoms may resolve completely within 48 hours of discontinuation. In moderate to severe SSLR, treatment with antihistamines, acetaminophen, NSAIDs, and glucocorticoids has been helpful. Antihistamines are often effective in treating pruritis and improving rash. Acetaminophen and NSAIDs are helpful for the arthralgias and low-grade fevers. Glucocorticoids alleviate severe symptoms such as high temperatures, severe arthritis or arthralgias, or more widespread rashes. Glucocorticoids are usually given PO unless severe discomfort or acute illness require IV administration. Prednisone is often dosed 0.5 to 1 mg/kg per day and Methylprednisolone 1 to 2 mg/kg per day. Occasionally higher dosing may be required.[11] Most cases improve with a 3-day course of glucocorticoids, and typically therapy is limited to one week.

Recommendations for future use of drugs within the same class or similar to the inciting agent is controversial. While some case reports indicate that patients were able to tolerate cefazolin after an SSLR to nafcillin[11] some specialists still recommend avoidance of all related drugs when possible.

Conclusion

Serum sickness-like reactions are often seen after drug exposure, most commonly cefaclor. Reactions can also be seen in association with infections and vaccines.[7] Serum sickness presents with rash, arthralgias, and lymphadenopathy. Fever is typically low-grade and may or may not be present.[5] Other findings include erythema and edema of the hands and feet, gastrointestinal disturbances, palpable purpura (vasculitis), and facial swelling. Although the patient may appear ill in the acute period, the disease is often benign and self-limited, with resolution within a few days to weeks. Treatment includes removal of the inciting agent and symptomatic treatment with antihistamines and glucocorticoids in moderate to severe cases.[11]

REFERENCES

1. **von Pirquet CF, Schick B**. (Die Serumkrankheit). Serum Sickness, Schick B (Ed), Williams & Wilkins, Leipzig 1905 (translation Baltimore 1951).
2. **Tatum AJ, Ditto AM, Patterson R**. Severe serum sickness-like reaction to oral penicillin drugs: three case reports. *Ann Allergy Asthma Immunol*. 2001 Mar; 86(3):330-4. PubMed PMID: 11289334.
3. **Yerushalmi J, Zvulunov A, Halevy S**. Serum sickness-like reactions. *Cutis*. 2002 May;69(5):395-7. PubMed PMID: 12041822.
4. **Yorulmaz A, Akın F, Sert A, Ağır MA, Yılmaz R, Arslan Ş**. Demographic and clinical characteristics of patients with serum sickness-like reaction. *Clin Rheumatol*. 2018 May;37(5):1389-1394. doi: 10.1007/s10067-017-3777-4. Epub 2017 Aug 9. PubMed PMID: 28795234.
5. **Knowles SR, Uetrecht J, Shear NH**. Idiosyncratic drug reactions: the reactive metabolite syndromes. *Lancet*. 2000 Nov 4;356(9241):1587-91. Review. PubMed PMID: 11075787.
6. **Platt R, Dreis MW, Kennedy DL, Kuritsky JN**. Serum sickness-like reactions to amoxicillin, cefaclor, cephalexin, and trimethoprim-sulfamethoxazole. *J Infect Dis*. 1988 Aug;158(2):474-7. PubMed PMID: 3261315.
7. **Ramsay M, Reacher M, O'Flynn C, Buttery R, Hadden F, Cohen B, Knowles W, Wreghitt T, Brown D**. Causes of morbilliform rash in a highly immunised English population. *Arch Dis Child*. 2002 Sep;87(3):202-6. PubMed PMID: 12193426; PubMed Central PMCID: PMC1719242.
8. **Chiong FJ, Loewenthal M, Boyle M, Attia J**. Serum sickness-like reaction after influenza vaccination. *BMJ Case Rep*. 2015 Dec 16;2015. pii: bcr2015211917. doi: 10.1136/bcr-2015-211917. PubMed PMID: 26677148; PubMed Central PMCID: PMC4691861.
9. **Kunnamo I, Kallio P, Pelkonen P, Viander M**. Serum-sickness-like disease is a common cause of acute arthritis

in children. *Acta Paediatr Scand*. 1986 Nov;75(6):964-9. PubMed PMID: 3564980.

10. **Zhang Z, Xiang Y, Wang B, Chen H, Cai X, Wang X, Mei L, Zheng Y**. Intestinal mucosal permeability of children with cefaclor-associated serum sickness-like reactions. *Eur J Pediatr*. 2013 Apr;172(4):537-43. doi: 10.1007/s00431-012-1926-y. Epub 2013 Jan 8. PubMed PMID: 23296953.
11. **Clark BM, Kotti GH, Shah AD, Conger NG**. Severe serum sickness reaction to oral and intramuscular penicillin. *Pharmacotherapy*. 2006 May;26(5):705-8. PubMed PMID: 16718943.

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