

# Serum Sickness–like Reactions

Joseph Yerushalmi, MD; Alex Zvulunov, MD; Sima Halevy, MD

*A serum sickness–like reaction (SSLR) to drug administration usually consists of cutaneous rash, arthralgia/arthritis, and, often, fever. This entity rarely has been discussed in the dermatologic literature. We describe the case of a 3-year-old girl with urticaria, fever, and arthralgia that appeared 8 days after starting cefaclor therapy for otitis media.*

Serum sickness was described first by von Pirquet<sup>1</sup> in 1905, following the use of horse serum containing diphtheria antitoxin. Serum sickness consists of fever, cutaneous eruption, arthralgia/arthritis, gastrointestinal disturbances, lymphadenopathy, and proteinuria. During the last decade, many authors have used the term *serum sickness–like reaction* (SSLR) to describe drug reactions that consist of rash, fever, and joint involvement often without evidence of cutaneous or systemic vasculitis. Generalized lymphadenopathy and proteinuria usually do not occur in SSLR. Unlike the serum sickness that is caused by circulating immune complexes, the pathophysiology of SSLR is not fully understood. An increasing number of drugs, including penicillins, cephalosporins, sulfonamides,<sup>2</sup> minocycline,<sup>3</sup> ciprofloxacin,<sup>4</sup> beta-blockers,<sup>5</sup> fluoxetine,<sup>6</sup> rifampin,<sup>7</sup> and others, have been implicated in the etiology of both serum sickness and SSLR.

## Case Report

A 3-year-old girl presented with a migratory pruritic rash, fever, and arthralgia of both ankles persisting for 24 hours. The patient had been treated with oral cefaclor, a cephalosporin antibiotic, during the previous 8 days for acute otitis media. On physical examination, the child was febrile (rectal temperature of 38°C), with swelling and tenderness of both feet and ankles that caused difficulty in walking. There were no signs of upper respiratory tract infection or otitis media. Multiple annular urticarial



Multiple annular plaques on the trunk of a 3-year-old girl.

plaques with dusky or clear centers, measuring 1 to 15 cm in diameter, were found on the face, trunk (Figure), and extremities. Mucous membranes were not involved.

Complete blood count results demonstrated leukocytosis (white blood cell count, 16,000/ $\mu$ L), with a normal differential count. The erythrocyte sedimentation rate was 25 mm/h. Results from blood cultures and serologic tests were negative for the Epstein-Barr virus, cytomegalovirus, and mycoplasma. Urine analysis was normal. Histopathologic examination of involved skin obtained from the trunk revealed dermal edema with mild perivascular lymphocytic infiltrate. Findings from the biopsy

From the Department of Dermatology, Soroka University Medical Center, Ben-Gurion University, Beer-Sheva, Israel.

Reprints: Sima Halevy, MD, Department of Dermatology, Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel (e-mail: halevy@bgumail.bgu.ac.il).

## Summarized Data of Reviewed Serum Sickness–like Reaction Cases\*

Source	Drug	No. of Cases	Latent Period, Days (mean)	Duration of SSLR, Days (mean)	Cutaneous Eruption Type	Fever, No. of Cases	Arthralgia/Arthritis, No. of Cases
Slama <sup>4</sup>	Ciprofloxacin	1	4	10	Urticaria	1	1
Yen et al <sup>5</sup>	Propranolol	1	†	13	Rash and angioedema	1	1
Vial et al <sup>11</sup>	Cefaclor	8	2–8 (6)	2–6 (3)	Urticaria	4	8
Hebert et al <sup>12</sup>	Cefaclor	12	2–10 (7)	†	Urticaria	†	10
Harel et al <sup>14</sup>	Minocycline	5	10–28 (17)	4–35 (14)	Urticaria	5	5
Lowery et al <sup>15</sup>	Cefprozil	4	1–9 (5)	10–25 (15)	Erythema multiforme	4	4

\*SSLR indicates serum sickness–like reaction.

†Not mentioned in referenced article.

specimen revealed no evidence of vasculitis. Histologic features were consistent with urticaria. The diagnosis of SSLR was based on the concomitant appearance of urticarial rash, fever, and arthralgia and was related to cefaclor therapy. Initial treatment with oral antihistamines showed no improvement. Subsequent treatment with prednisone (1 mg/kg per day) resulted in a rapid and complete resolution of the rash and clinical symptoms. Prednisone was discontinued after 3 days, without recurrence of symptoms.

### Comment

Some doubt still exists about SSLR and its pathogenesis. Many authors use this term to describe an adverse drug reaction of type III hypersensitivity, which is characteristic of the true serum sickness disease.<sup>8,9</sup> Kunnamo et al<sup>10</sup> found circulating immune complexes in the sera of 12 of 15 patients with SSLR, mostly associated with the use of penicillin. On the other hand, in many reports of SSLR mostly related to cefaclor therapy, immune complexes were not considered in the pathogenesis.<sup>11,12</sup> A graft-versus-host–like reaction as proposed by Gleichmann et al<sup>13</sup> has been adopted by some authors as the pathogenesis of SSLR.<sup>11</sup> According to this hypothesis, the drug or its metabolites bind to membrane determinants of patients' cells, which provokes cell-mediated immunity after being recognized as “non-self.”

We reviewed 31 cases of SSLR that were described in sufficient detail in the literature and that were not suggestive of antigen-antibody complex formation (ie, true serum sickness). Cases with palpable purpura, alterations in complement's concentration, or other indications of vasculitis were not included. The data are presented in the Table.

Cefaclor (as suspension formulation used in pediatric medicine) is the most prevalent drug implicated in the SSLR cases (20 of 31). In general, SSLR occurred within 2 to 10 days after beginning therapy with the trigger drug, although lag periods as long as 28 days also were reported.<sup>14</sup> Cutaneous eruptions associated with SSLR included urticaria, angioedema, and erythema multiforme. Sometimes, the described urticarial lesions have dusky-to-purple centers, as in our case, and resemble erythema multiforme. Twenty-five of the 31 cases reviewed manifested urticaria. As biopsies of the skin were not performed in most of the cases, urticarial vasculitis cannot be ruled out. Also, it is remarkable that in some reports, nonspecific terms (eg, erythematous rash) are used to describe cutaneous involvement.<sup>5</sup> Joint involvement (arthralgia/arthritis) was present in 29 of the 31 cases, mostly polyarticular, affecting joints such as ankles, wrists, hands, and knees. SSLR related to cefaclor was described in 12 children by Hebert et al<sup>12</sup> in 1991. Joint involvement in these children was manifested as edema, decreased range of motion,

warmth, and pain. In most patients, these symptoms may be related to skin edema around the affected joints due to urticaria rather than arthritis.

Generally, SSLR has a benign clinical course and resolves in a few days, though cases of several weeks' duration also have been reported. Antihistamines and steroids have been used in some patients with satisfactory results, though controlled clinical data have not been reported.

SSLR describes drug reactions with a broad dermatologic spectrum accompanying fever and arthralgia/arthritis. Palpable purpura (vasculitis), urticarial lesions, and erythema multiforme-like lesions all have been reported in SSLR. Possibly, these different presentations may reflect different pathogenesis. Thus, further definition and study of this entity are needed.

## REFERENCES

1. Von Piruet CF, Schick B. *Die Serumkrankheit*. Leipzig: Deuticke; 1905.
2. Platt R, Dreis MW, Kennedy DL, et al. Serum sickness-like reactions to amoxicillin, cefaclor, cephalexin and trimethoprim-sulfamethoxazole. *J Infect Dis*. 1988;158:474-477.
3. Puyana J, Urena V, Quirce S. Serum sickness-like syndrome associated with minocycline therapy. *Allergy*. 1990;45:313-315.
4. Slama TG. Serum sickness-like illness associated with ciprofloxacin. *Antimicrob Agents Chemother*. 1990;34:904-905.
5. Yen MC, Piszczek JE, Mintzer DL. Serum sickness-like syndrome associated with propranolol therapy. *Postgrad Med*. 1983;74:291-294.
6. Miller LG, Bowman RC, Mann D. A case of fluoxetine-induced serum sickness. *Am J Psychiatry*. 1989;146:1616-1617.
7. Parra FM, Perez-Elias MJ, Cuevas M. Serum sickness-like illness associated with rifampicin. *Ann Allergy*. 1994;73:123-125.
8. Creamer JD, McGrath JA, Webb-Peploe M, et al. Serum sickness-like illness following streptokinase therapy: a case report. *Clin Exp Dermatol*. 1995;20:468-470.
9. Bisceglia M, Germani G, Tardio B, et al. Leukocytoclastic vasculitis of the colon. *Ital J Surg Sci*. 1989;19:269-272.
10. Kunnamo I, Kallio P, Pelkonen P. Serum sickness-like disease is a common cause of acute arthritis in children. *Acta Paediatr Scand*. 1986;75:964-969.
11. Vial T, Pont J, Descotes J, et al. Cefaclor-associated serum sickness-like disease: eight cases and review of literature. *Ann Pharmacother*. 1992;26:910-913.
12. Hebert AA, Levy ML, Sigman ES, et al. Serum sickness-like reactions from cefaclor in children. *J Am Acad Dermatol*. 1991;25:805-808.
13. Gleichmann E, Pals ST, Rolink AG, et al. Graft-versus-host reactions: clues to the etiopathology of a spectrum of immunological diseases. *Immunol Today*. 1984;5:324-332.
14. Harel L, Amir J, Livni E, et al. Serum sickness-like reaction associated with minocycline therapy in adolescents. *Ann Pharmacother*. 1996;30:481-483.
15. Lowery N, Kearns GL, Young RA, et al. Serum sickness-like reactions associated with cefprozil therapy. *J Pediatr*. 1994;125:325-328.