

Serum sickness-like drug reaction: two cases with a neutrophilic urticarial pattern

The diagnosis of serum sickness-like reaction (SSLR) is typically based on clinical findings. Histopathologic examination is often deferred, as these eruptions commonly present in young children, and often to primary care providers. A PubMed literature search revealed only five existing cases of SSLR which describe cutaneous histopathologic features. We report two cases of SSLR, one each to bupropion and cefazolin. Skin biopsy findings in both cases showed a neutrophil-predominant urticarial pattern resembling neutrophilic urticaria or neutrophilic urticarial dermatosis. We also provide a summary of the histopathologic findings that can help support a diagnosis of SSLR.

Keywords: bupropion, cefazolin, cutaneous drug reaction, neutrophilic dermatoses, serum sickness-like reaction

Nguyen CV, Miller DD. Serum sickness-like drug reaction: two cases with a neutrophilic urticarial pattern.

J Cutan Pathol 2017; 44: 177–182. © 2016 John Wiley & Sons A/S.
Published by John Wiley & Sons Ltd

**Cuong V. Nguyen and
Daniel D. Miller**

Department of Dermatology, University of
Minnesota, Minneapolis, MN, USA

Cuong V. Nguyen,
Department of Dermatology, University of
Minnesota, 516 Delaware Street Southeast, Mail
Code 98, Phillips-Wangensteen Building, Suite
4-240, Minneapolis, MN 55455, USA
Tel: 612-625-8625
Fax: 612-624-6678
e-mail: nguy2291@umn.edu

Accepted for publication November 8, 2016

Serum sickness-like reaction (SSLR) is a well-recognized adverse medication reaction most often diagnosed by clinical findings. The majority of cases are evaluated by non-dermatologists, or present in pediatric patients, in whom skin biopsy is often deferred. A search in PubMed (www.pubmed.org) from January 1, 1951 to December 31, 2015 with keywords including 'serum sickness-like' and 'serum sickness-like reaction' revealed over 200 case reports of SSLR. We analyzed all relevant articles for descriptions of SSLR histopathology. To date, only five of these cases have reported biopsy results (Table 1).^{1–5} As such, the histopathology of SSLR is underreported and poorly understood. Most dermatopathology textbooks either exclude discussion of SSLR or describe it in association with true serum sickness.⁶ We report two cases of SSLR with a neutrophilic urticarial pattern and review the literature

to further characterize the histopathology of SSLR.

Case 1

A 24-year-old Caucasian male was admitted to the hospital with a 3-day history of painful, urticarial plaques and arthralgia 1 month after starting bupropion. The rash started on his left wrist and continued to progress despite intravenous methylprednisolone 125 mg, followed by 2 days of 60 mg of oral prednisone daily. Biopsy was obtained 3 days following the first systemic steroid treatment.

Physical examination revealed a 5 cm in diameter, annular and erythematous plaque with central dusky discoloration of the left ventral forearm (Fig. 1). Similar edematous and urticarial plaques were present on the right forearm, scalp and medial feet. There was joint tenderness of



Fig. 1. Urticarial, annular plaques with dusky centers on the ventral forearm.

the wrists, fingers, knees and ankles. Pictures provided by the patient from the day of onset revealed asymmetric upper lip swelling; there was no facial or extremity edema at the time of exam. The patient had gone camping 1 month prior in northern Minnesota, an area endemic for *Ixodes scapularis* ticks. The clinical differential diagnosis included SSLR, urticarial hypersensitivity reaction, pressure urticaria, urticarial vasculitis and erythema migrans.

Laboratory findings were pertinent for white blood cell count of 16,000/1 (87.2% neutrophils) while on prednisone. There was no peripheral eosinophilia. Liver function tests were within normal limits. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were within normal limits, as were C3 and C4 complement levels. Urinalysis was negative for proteinuria or hemoglobinuria. Lyme and *Babesia* antibody titers were negative.

Biopsy of the left ventral forearm plaque (Fig. 2) revealed a superficial and mid-perivascular and interstitial mixed cell infiltrate with prominent interstitial neutrophils and occasional eosinophils. Perieccrine neutrophils were noted within the mid-dermis. Interspersed between collagen fibers was an amorphous, stringy, bluish material suspected to represent neutrophil degranulation (Figs. 3 and 4); colloidal iron failed to stain this material. The findings were interpreted as an urticarial dermatosis that resembled neutrophil-rich urticaria, which is in the context of the patient's clinical findings, was consistent with a SSLR.

Case 2

A 74-year-old Caucasian male with history of undifferentiated spondyloarthropathy

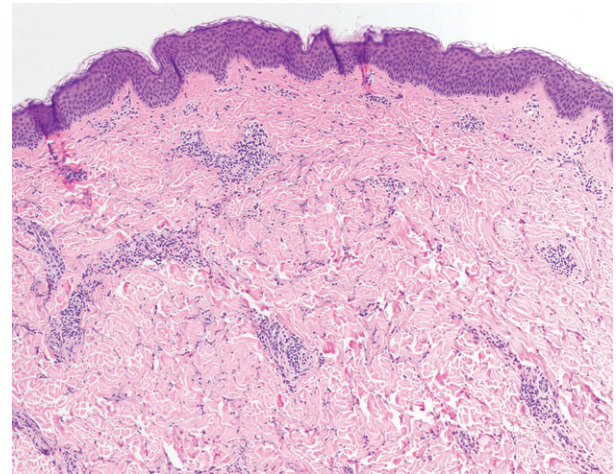


Fig. 2. Superficial and mid-perivascular and interstitial infiltrate (hematoxylin and eosin stain, ×100 magnification).

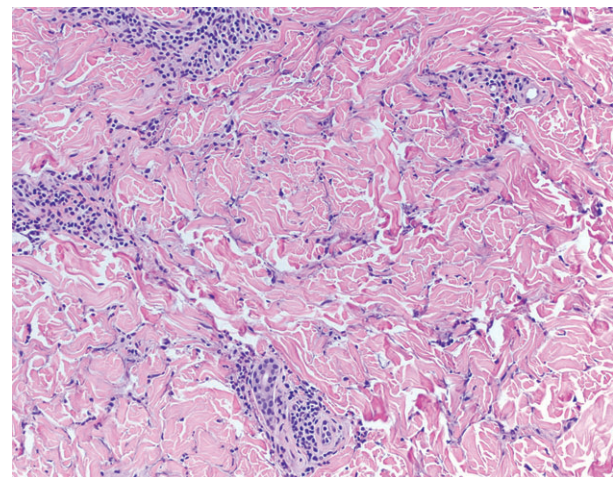


Fig. 3. Prominently interstitial mixed infiltrate of neutrophils and scattered eosinophils (×200 magnification).

presented to the hospital 3 days after knee replacement surgery with a 6-day history of pruritus that progressed to painful urticarial plaques. He also endorsed arthralgia and had a fever to 102°F on admission. Of note, the patient had had a similar reaction several days following a surgery in 2013. In both instances, he had received intravenous cefazolin perioperatively.

Physical examination revealed facial edema and eyelid swelling. Pink, edematous, annular plaques with central dusky discoloration were present on the trunk and extremities (Fig. 5). Extending onto the lateral fingers were tender, serpiginous and hemorrhagic-appearing and edematous papules (Fig. 6). Three punch biopsies were obtained from these hemorrhagic-appearing areas for pathology,

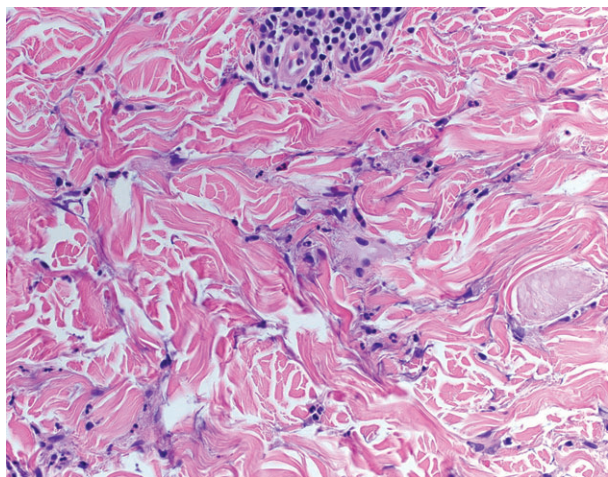


Fig. 4. Amorphous, stringy, blue material between collagen fibers with associated neutrophils, suspected to represent neutrophil degranulation (×400 magnification).

direct immunofluorescence and tissue culture. The clinical differential diagnosis of annular and urticarial erythema, especially those with dusky or ecchymotic central components, included SSLR, urticaria multiforme, urticarial vasculitis, eosinophilic annular erythema, angioinvasive soft tissue infection and Schnitzler syndrome.

Laboratory findings were pertinent for a white blood cell count of 13,700/l with no peripheral eosinophilia. Liver function tests remained within normal limits. The patient initially presented with normal kidney function, but developed acute kidney injury that improved with fluid resuscitation. CRP was elevated to 160.0 mg/l, but ESR remained within normal limits. Rheumatologic work-up was unremarkable with negative anti-nuclear antibody (ANA), anti-dsDNA, anti-neutrophil cytoplasmic antibody (ANCA) panel, anti-Ro, anti-La and anti-phospholipid antibodies. Blood and tissues cultures remained negative for bacteria and fungus.

Histopathology revealed slight spongiosis above a superficial and deep perivascular and interstitial infiltrate of primarily neutrophils with scattered lymphocytes and eosinophils. There was scant perivascular leukocytoclasia, but no other features of vasculitis. Neutrophils were easily identified around adnexal structures. Amorphous bluish material was seen between collagen fibers; colloidal iron staining was negative for dermal mucin deposition (Fig. 7). Special stains for microorganisms including periodic acid-Schiff, Grocott's methenamine silver, Fite and Gram stains were negative. This



Fig. 5. Urticarial plaques with central dusky discoloration on the back and upper extremities.

histologic pattern was interpreted as resembling neutrophil-rich urticaria or NUD, and based on clinicopathologic correlation was considered consistent with SSLR.

Discussion

Serum sickness is a systemic immunologic reaction first described in 1905 by von Pirquet and Schick.⁷ Children developed fever, arthralgia, lymphadenopathy and cutaneous eruptions 8–12 days after subcutaneous injection with horse serum containing diphtheria antitoxin. Urticarial eruptions, occurring in approximately 91% of cases, represented the most common cutaneous finding.⁸ Less commonly, patients also presented with morbilliform and purpuric rashes. A prospective clinical study confirmed the presence of circulating serum immune complexes, and perivascular deposits on direct immunofluorescence testing of the skin of patients with serum sickness.⁹ Skin biopsies of these patients revealed limited lymphocytic and histiocytic perivascular infiltrates with only rare neutrophils. Fibrinoid necrosis was not found in any of the 13 biopsies, although there have been subsequent reports of true small vessel



Fig. 6. Serpiginous and hemorrhagic-appearing papules extending along the lateral digits.

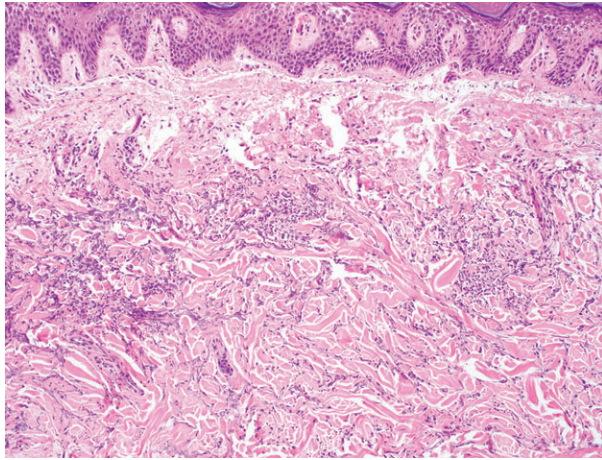


Fig. 7. Superficial and deep perivascular and interstitial neutrophil-rich infiltrate (hematoxylin and eosin stain, $\times 100$ magnification).

vasculitis in serum sickness.⁷ Patients often exhibit a decline in serum complement levels (C3 and C4) on serial measurements. Because of the development of immune complexes, other organ systems can be involved. Proteinuria is reported in up to 67% of patients,⁹ although kidney involvement typically does not result in renal failure.

Unlike serum sickness, a type III hypersensitivity reaction, SSLR is thought not to form immune complexes, although the pathogenesis of medication-induced SSLR is poorly understood

Table 1. Clinical and histopathologic features of patients with serum sickness-like reaction

Clinical features	Case 1					Case 2					Swanson and English ²					Yerushalmi et al. ³					Landau et al. ⁴					Parra et al. ⁵				
	Age	Gender	Urticarial	Morbiliform		Age	Gender	Urticarial	Morbiliform		Age	Gender	Urticarial	Morbiliform		Age	Gender	Urticarial	Morbiliform		Age	Gender	Urticarial	Morbiliform		Age	Gender	Urticarial	Morbiliform	
Patient demographics																														
Presumed culprit drug																														
Clinical morphology																														
Histopathologic features																														
Pattern of infiltrate																														
Infiltrate cell type																														
Epidermal edema																														
Dermal edema																														
Level of dermal involvement																														
TMP-SMX, trimethoprim-sulfamethoxazole																														

Serum sickness-like drug reaction: two cases with a neutrophilic urticarial pattern

Table 2. General features of serum sickness reaction versus serum sickness-like reaction

		Serum sickness reaction	Serum sickness-like reaction
Pathogenesis		Type III hypersensitivity	Non-immune complex mediated
Drug culprit		Exogenous proteins	Non-protein mediated
Days until onset		8–12	7–21
Clinical features	Rash	+	+
	Fever	+	+
	Arthralgia	+	+
	Lymphadenopathy	+	+/-
	Systemic involvement	+	+/-
Laboratory features	Hypocomplementemia	+	+/-
	Eosinophilia	+/-	+/-
	Proteinuria	+	-
Histopathologic features	Perivascular infiltrate	+	+
	Neutrophils	Rare	+/-
	Direct immunofluorescence	+/-	-

(Table 2). Seven to twenty-one days following drug exposure, patients present similar to true serum sickness with an urticarial or morbilliform eruption, arthralgia and fever.¹⁰ There is typically no internal organ involvement.

There are only five previous reports describing the histopathology of SSLR. While bupropion and cefazolin are well-documented culprits of SSLR, this is the first case series to describe their histopathologic findings.^{11–13} Existing descriptions of biopsy findings in SSLR appear relatively non-specific, but fall within the spectrum of urticarial dermatoses. The current cases showed a subtle but notable interstitial neutrophil predominance, which resembled neutrophilic urticaria or NUD, as well as interstitial bluish material similar to that seen in interstitial granulomatous dermatitis.

In 2009, NUD was proposed as a distinct clinical and histopathologic diagnosis from neutrophilic urticaria.¹⁴ Systemic symptoms were common in NUD, with fevers in 66.7% and polyarthralgia in 77.8% of patients.¹⁴ Unlike neutrophilic urticaria, the majority of patients with NUD had an associated underlying systemic inflammatory disease, most commonly systemic lupus erythematosus, adult-onset Still's disease or Schnitzler syndrome. On histopathology, NUD presents with a more prominent interstitial neutrophilic infiltrate than neutrophilic urticaria,¹⁴ and often, subtle interstitial amorphous bluish material.^{14,15} The two SSLR cases described here show these features, as well as tropism of neutrophils for eccrine glands. This finding (termed 'neutrophilic epitheliotropism') was recently described in NUD, with a sensitivity of 83.1% and specificity of

74.3% for this diagnosis.¹⁶ SSLR also exhibits many systemic symptoms similar to NUD, and thus we posit that SSLR may be an acute systemic reaction similar to NUD, but triggered by a medication rather than an underlying inflammatory disease.

Other histopathologic considerations for this neutrophilic urticarial pattern include non-bullous neutrophilic lupus erythematosus, Still's disease, cryopyrin-associated periodic syndrome and Schnitzler's syndrome.^{17–20} The prompt resolution of symptoms with drug cessation in both cases ruled out these other recurrent and chronic diseases. An urticarial hypersensitivity-type drug reaction is also in the differential, but the clinical findings here were both strikingly those of SSLR. Unlike urticarial vasculitis and (occasionally) true serum sickness, patients with SSLR do not exhibit evidence of vasculitis. Direct immunofluorescence (DIF) testing in case 2 did not reveal vascular or perivascular deposits of immunoglobulins, C3 or fibrinogen.

In conclusion, we describe the clinical and histopathologic findings in two adult cases of SSLR to bupropion and cefazolin, to expand the range of described biopsy findings in SSLR. These histopathologic changes appear consistently urticarial in existing reports, but are not entirely specific to this diagnosis. SSLR may share overlapping microscopic features with neutrophilic urticaria and other neutrophilic dermatoses, especially those associated with connective tissue diseases. Proper diagnosis requires careful clinicopathologic correlation.

References

1. Tolpinrud WL, Bunick CG, King BA. Serum sickness-like reaction: histopathology and case report. *J Am Acad Dermatol* 2011; 65: e83.
2. Swanson JK, English JC. Serum sickness-like reaction to Pamabrom. *J Drugs Dermatol* 2006; 5: 284.
3. Yerushalmi J, Zvulunov A, Halevy S. Serum sickness-like reactions. *Cutis* 2002; 69: 395.
4. Landau M, Shachar E, Brenner S. Minocycline-induced serum sickness-like reaction. *J Eur Acad Dermatol Venereol* 2000; 14: 67.
5. Parra FM, Pérez Elias MJ, Cuevas M, Ferreira A. Serum sickness-like illness associated with rifampicin. *Ann Allergy* 1994; 73: 123.
6. Brinster N. Cutaneous adverse reactions to drugs. In: Calonje E, Brenin T, Lazar A, McKee PH, eds. *McKee's pathology of the skin with clinical correlation*, 4th ed. Philadelphia, PA, USA: Elsevier Saunders, 2012; 594.
7. von Pirquet C, Schick B. Serum sickness. Baltimore: Williams & Wilkins, 1951.
8. Kojis F. Serum sickness and anaphylaxis. *Am J Dis Child* 1942; 64: 93.
9. Bielory L, Gascon P, Lawley TJ, Young NS, Frank MM. Human serum sickness: a prospective analysis of 35 patients treated with equine anti-thymocyte globulin for bone marrow failure. *Medicine (Baltimore)* 1988; 67: 40.
10. Mathur AN, Mathes EF. Urticaria mimickers in children. *Dermatol Ther* 2013; 26: 467.
11. Davis JS, Boyle MJ, Hannaford R, Watson A. Bupropion and serum sickness-like reaction. *Med J Aust* 2001; 174: 479.
12. McCollom RA, Elbe DH, Ritchie AH. Bupropion-induced serum sickness-like reaction. *Ann Pharmacother* 2000; 34: 471.
13. Brucculeri M, Charlton M, Serur D. Serum sickness-like reaction associated with cefazolin. *BMC Clin Pharmacol* 2006; 6: 3.
14. Kieffer C, Cribier B, Lipsker D. Neutrophilic urticarial dermatosis. *Medicine (Baltimore)* 2009; 88: 23.
15. Gusdorf L, Bessis D, Lipsker D. Lupus erythematosus and neutrophilic urticarial dermatosis. *Medicine (Baltimore)* 2014; 93: e351.
16. Broekaert SMC, Bøer-Auer A, Kerl K, et al. Neutrophilic epitheliotropism is a histopathological clue to neutrophilic urticarial dermatosis. *Am J Dermatopathol* 2016; 38: 39.
17. Gleason BC, Zembowicz A, Granter SR. Non-bullous neutrophilic dermatosis: an uncommon dermatologic manifestation in patients with lupus erythematosus. *J Cutan Pathol* 2006; 33: 721.
18. Criado RFJ, Criado PR, Vasconcellos C, et al. Urticaria as a cutaneous sign of adult-onset Still's disease. *J Cutan Med Surg* 2006; 10: 99.
19. Kolivras A, Theunis A, Ferster A, et al. Cryopyrin-associated periodic syndrome: an autoinflammatory disease manifested as neutrophilic urticarial dermatosis with additional perieccrine involvement. *J Cutan Pathol* 2011; 38: 202.
20. Simon A, Asli B, Braun-Falco M, et al. Schnitzler's syndrome: diagnosis, treatment, and follow-up. *Allergy* 2013; 68: 562.