Title: To Test or Not to Test? How a Positive Rapid Strep Test May Perplex the Diagnosis of Serum Sickness-Like Reaction in a Case Report

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Highlights:

1. Serum sickness-like reaction (SSLR) is a rare immunologic disorder with unclear pathogenesis related to serum sickness, a type III hypersensitivity reaction.

2. The clinical presentation of SSLR includes fever, arthralgia, and maculopapular or urticarial rash mimicking sepsis.

3. Rapid Strep Test (RST) must be used cautiously, mainly in patients with clinical suspicion of pharyngitis and Centor score of 3 or more.

4. SSLR is a clinical diagnosis and a false-positive RST may misguide the management of these patients.

5. The prognosis of SSLR is excellent and the treatment is symptomatic, but severe cases may lead to unnecessary hospitalization, antibiotic treatment and diagnostic testing.

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ABSTRACT

Background: Serum sickness-like reaction (SSLR) is a rare cause of drug eruption. The clinical presentation includes fever, rash, and arthralgia which typically occurs 1-2 weeks after the administration of common antibiotics such as amoxicillin or cefaclor. It is a challenging diagnosis because it mimics sepsis and other exanthematous diseases. Rapid Strep Test (RST) is a useful diagnostic test for detecting *Streptococcus pyogenes* in patients with pharyngitis and Centor score of 3 or more guiding the administration of antibiotics.

The Case: We report a case of a 63-year-old female patient seen in the emergency department (ED) with high-grade fever, diffuse rash, musculoskeletal pain, and a positive RST without clinical evidence of pharyngitis. The primary care physician ordered the RST before the referral to the ED to investigate the febrile rash without a clear indication, misleading to the diagnosis of streptococcal sepsis. She was eventually diagnosed with SSLR and she was treated with corticosteroids, leading to rapid symptomatic relief.

Conclusion: SSLR is an interesting clinical entity, and its pathogenesis is poorly understood. This case emphasizes that SSLR is a clinical diagnosis of exclusion after ruling out other similar disorders. Physicians should be familiar with this benign condition to avoid unnecessary diagnostic testing such as RST which may misguide diagnosis and treatment. Simple diagnostic tests should be used with caution under certain indications; misuse of RST can cause false-positive results, complicating the management of these cases.

Key Words: Serum Sickness; Exanthema; Drug Eruption; Amoxicillin; *Streptococcus pyogenes* (Source: MeSH-NLM).

INTRODUCTION

Adverse cutaneous drug reaction is a common cause of Emergency Department (ED) visits or hospital admissions.[1] Serum sickness-like reaction (SSLR) is a rare cause of this common diagnostic problem.[2-5] It is usually triggered by beta-lactam antibiotics (especially amoxicillin and cefaclor).[2-8,12] Other drugs such as analgesics, vaccinations, and infectious diseases trigger SSLR less often.[2,4,7,8,9,12] SSLR usually occurs 1-2 weeks after the exposure, but this is variable (0-21 days).[2,5-7] The classic triad is fever, diffuse arthralgia and rash, although renal involvement and lymphadenopathy may also occur.[2,-5,7,8,12] The rash is diffusely located over the trunk and extremities with maculopapular or urticarial morphology and may be occasionally pruritic.[2,4,5,9]

Streptococcus pyogenes is the most common cause of bacterial pharyngitis, although viral pharyngitis is generally more common.[10] Rapid strep test (RST) is useful for the diagnosis of pharyngitis caused by *S. pyogenes*, with a specificity of over 90%. RST should be ordered in patients who present with pharyngitis and Centor score of 3 or more.[10] However, simple carriage of *S. pyogenes* may give a positive RST result in patients without pharyngitis, hence misguiding their management.[10,11] Overdiagnosis of streptococcal infections and overuse of antibiotics are possible consequences of false-positive RST, especially when the clinical presentation is unclear and the previously outlined requirements do not apply.

In this report, we present an unusual case of SSLR without clinical evidence of pharyngitis and a positive RST, following treatment of respiratory tract infection with amoxicillin/clavulanate and analgesics.

CASE REPORT

A 63-year-old woman presented to the Emergency Department with diffuse rash, high-grade fever, chills, diffuse musculoskeletal pain, and a positive RST performed by her physician despite the absence of throat pain. Past medical and epidemiological history was unremarkable except for a respiratory tract infection (RTI) 12 days ago treated with amoxicillin/clavulanate (7-day course), acetaminophen, and ibuprofen. Ibuprofen was administered for the last 3 days only. No recent travel or exposure to other infectious agents was reported. The rash was neither painful nor pruritic and was diffusely spread, sparing the face, the palms, and the soles, with a maculopapular pattern and occasional urticarial-like plaques (Figure 1). The rest of the physical examination, including the head and neck examination, was unremarkable. She developed the aforementioned symptoms the day before the ED visit. Laboratory tests revealed normochromic normocytic anemia (Hb 11.2 g/dl), normal white blood cells (WBCs) with a neutrophilic predominance (9.94 K/μl with 94.1 % neutrophils), elevated C-reactive protein (CRP) (44.7 mg/dL), elevated erythrocyte sedimentation rate (ESR) (75 mm/h) and elevated ferritin (1546 ng/ml). Renal function (urea 24 mg/dl and creatinine 0.7 mg/dl) and urinalysis were normal. Cardiac evaluation with an electrocardiogram and echocardiogram was unremarkable. Liver function tests, C3, and C4 levels were normal. Antistreptolysin O titer (ASTO), rapid plasma reagin test (RPR), blood cultures, and serological tests for antibodies against viruses and rickettsiae were negative. Clindamycin was administered for coverage of *S. pyogenes*, based on the positive RST and the clinical suspicion of sepsis, but was discontinued due to diarrhea. The lack of response to clindamycin and the negative microbiological work-up reduced the suspicion of streptococcal infection. Hence, additional antibiotics were not considered.

The clinical findings and the negative diagnostic work-up raised suspicion of adverse drug reactions. The patient was eventually diagnosed as suffering from a serum-sickness like reaction (SSLR) caused by the treatment of RTI 1-2 weeks before the development of her symptoms. The most likely trigger was amoxicillin, although clavulanate and ibuprofen cannot be excluded.[2] Methylprednisolone 0.5 mg/kg per os was administered, resulting in the resolution of symptoms after 2 days, while the dose was gradually tapered over one week.

DISCUSSION

SSLR is an immunologic disorder that usually occurs 1 to 2 weeks after the administration of a drug. The most common triggers are amoxicillin and cefaclor.[2-8] The pathogenesis is not fully understood, although factors related to the immune system, age, drug metabolism, and infectious agents are considered essential for the development of SSLR.[2-3] Re-exposure to cefaclor increases the risk of developing SSLR, which does not apply to amoxicillin.[3,5] However, SSLR is not associated with atopy, hence, it is not considered a part of the type I hypersensitivity reactions spectrum.[5] SSLR is more common in pediatric patients, but this observation might be explained by the fact that children are more likely to be diagnosed with respiratory tract infections and treated with antibiotics than adults.[2,3,6,12] Infectious agents such as viruses and bacteria can precipitate the development of drug-induced rash.[2] This theory may explain the close relationship between SSLR and antibiotics.[2] In our case, amoxicillin/clavulanate was more likely the trigger of SSLR, because SSLR usually develops 1-2 weeks after the administration of the responsible drug. Amoxicillin/clavulanate was administered 11 days before the development of SSLR, but ibuprofen was administered 2 days before SSLR. However, the clinical presentation of the patient and the positive RST initially misled the diagnosis and urged the attending physician to (unnecessarily) administer clindamycin.

The original version of this hypersensitivity reaction is serum sickness (SS) which occurs after the administration of heterologous antitoxins such as antitetanus or antirabies serum.[4-8,12] True serum sickness is a type III hypersensitivity reaction that commonly involves the lymph nodes and the internal organs such as the kidneys, in contrast to the SSLR.[2-7,12] The pathogenesis of SS explains the vasculitis and the low levels of complement which are typically normal in SSLR, like in our case.[2,3,4,6,9,12]

The diagnosis of SSLR is mainly clinical. Key points include a diffuse maculopapular or urticarial rash, fever, and arthralgia, although the classic triad is not always present.[2-4,6,8,9,12] Laboratory studies commonly reveal elevated inflammatory markers (ESR, CRP), elevated WBCs with neutrophilic predominance, thrombocytosis, and anemia.[6,9,12] Renal involvement may be present with hematuria and proteinuria.[9] However, these findings are neither sensitive nor specific to this condition. More severe cases are misdiagnosed as sepsis, leading to unnecessary empiric antibiotic treatment[7]. The rash of SSLR mimics other common skin disorders such as urticaria, erythema multiforme, and viral exanthems.[2,3]

The course of SSLR is generally benign, hence the treatment is mostly symptomatic.[2,3,8,9,12] The most important step is to discontinue the responsible medication.[4,7,12] Although the treatment remains controversial, there is limited evidence that supports the administration of acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), antihistamines, and fluids.[2,4,7,12] It must be noted that analgesics are responsible for a minority of SSLR cases, so they must be used with caution.[2,6,8] Corticosteroids are reserved for severe cases such as in our patient[2,7,12]. Although there is a small risk of beta-lactam cross-reactivity in patients with SSLR, there is limited evidence to suggest avoidance of other beta-lactam antibiotics.[3]

Viruses usually cause pharyngitis, but *S. pyogenes* is the most common bacterial pathogen.[10] The initial step is the calculation of the Centor score (TABLE 1), which is correlated with the pre-test probability of streptococcal pharyngitis.[10,11] RST is a first-line test for the differentiation between viral and bacterial pharyngitis; current guidelines suggest testing with RST in patients with a Centor score of 3 or more.[10] However, this guideline does not apply to individuals without pharyngitis, as a positive test result is likely to be false due to the asymptomatic carriage of *S. pyogenes.* The positive RST in this patient with the febrile rash raised the suspicion of streptococcal complications.

The differential diagnosis in a febrile patient with rash, arthralgia, and positive RST is broad and challenging. The lack of facial rash, strawberry tongue, sandpaper texture, and Pastia lines make the diagnosis of scarlet fever unlikely.[13] The absence of cardiac involvement, arthritis, and other criteria of acute rheumatic fever, including the serpiginous morphology of erythema marginatum, make this diagnosis unlikely in a patient above the age of 40 years.[14] Urticaria causes pruritus while the fever and malaise are absent.[2,3,9] The rash of erythema multiforme is associated with pain, pruritus, palmoplantar distribution, targetoid lesions, and blistering which are not present in this case.[2,3,9] Absence of eosinophilia, elevated transaminases, lymphadenopathy, and facial rash or edema in conjunction with the presence of generalized arthralgias and short latency period (less than 2-6 weeks), make the diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS) unlikely.[8] Adult-onset Still's disease which is associated with spiking fever, hyperferritinemia, neutrophilia, and episodic salmon-like colored rash with fever spikes, may be ruled out by the constant presence of the rash.[15] Infectious diseases - associated rash may be ruled out by serological tests and similarly, acute interstitial nephritis is excluded by the absence of renal involvement, when renal function and urine analysis appear normal.

Physicians should be aware of the SSLR as a clinical entity and should maintain a high clinical suspicion index in patients presenting with fever and rash after a recent exposure to antibiotics. This case report emphasizes the importance of clinical diagnosis and reasonable use of even simple diagnostic tests like RST, which may be misleading when performed without a clear clinical indication, to avoid unnecessary diagnostic testing, hospitalization, and antibiotic treatment.[4,7] The restricted use of antibiotics in patients with immunologic disorders is essential to avoid delayed diagnosis and treatment.[4,7]

SUMMARY-ACCELERATING TRANSLATION

Να Κάνουμε Τεστ ή να Μην Κάνουμε; Πώς ένα θετικό Rapid Strep Test Μπορεί να Περιπλέξει τη Διάγνωση της Αντίδρασης Δίκην Ορονοσίας

Η αντίδραση δίκην ορονοσίας αποτελεί ένα σπάνιο αίτιο εμπύρετου εξανθήματος. Η κλινική εικόνα ποικίλει και περιλαμβάνει εξάνθημα, πυρετό και αρθραλγία/αρθρίτιδα, τα οποία παρατηρούνται 1-2 εβδομάδες μετά την έκθεση σε φαρμακευτικούς ή/και λοιμογόνους παράγοντες. Θεωρείται δύσκολη διάγνωση, επειδή πρόκειται για σπάνια οντότητα και μιμείται τη σήψη και άλλες εξανθηματικές νόσους. Η διάγνωση είναι κλινική και τίθεται μετά από τον αποκλεισμό λοιμωδών και ανοσολογικών παθήσεων με παρόμοια κλινική εικόνα.

Η φαρυγγίτιδα συνήθως είναι ιογενούς αιτιολογίας και δε χρήζει αντιβιοτικής αγωγής, αλλά ο *Streptococcus pyogenes* είναι το πιο κοινό αίτιο βακτηριακής φαρυγγίτιδας. Η στρεπτοκοκκική φαρυγγίτιδα πρέπει να καταπολεμάται με αντιβιοτικά για την αποφυγή σοβαρών επιπλοκών. Το rapid strep test (RST) αποτελεί μία χρήσιμη διαγνωστική εξέταση για την ανίχνευση του *Streptococcus pyogenes* σε ασθενείς με φαρυγγίτιδα και Centor score 3 ή παραπάνω καθοδηγώντας τη χορήγηση αντιβιοτικών. Ωστόσο, η κατάχρηση του μπορεί να οδηγήσει σε ψευδώς θετικά περιστατικά περιπλέκοντας την κλινική διαχείριση, όπως συνέβη στο περιστατικό μας.

Παρουσιάζουμε το ενδιαφέρον περιστατικού μίας ασθενούς 63 ετών, η οποία προσήλθε στο Τμήμα Επειγόντων Περιστατικών με διάχυτο εξάνθημα, υψηλό εμπύρετο και διάχυτο μυοσκελετικό άλγος. Αξίζει να σημειωθεί ότι είχε προηγηθεί παραπομπή της ασθενούς από το γενικό ιατρό, ο οποίος πραγματοποίησε RST με θετικό αποτέλεσμα. Το εξάνθημα παρουσίασε κνιδωτική και κηλιδοβλατιδώδη μορφολογία, ήταν ανώδυνο, χωρίς κνησμό και δεν εμφανιζόταν στην περιοχή του προσώπου, των παλαμών και των πελμάτων. Η φυσική εξέταση δεν ανέδειξε άλλα ευρήματα. Το ατομικό αναμνηστικό και το επιδημιολογικό ιστορικό της ασθενούς ήταν ελεύθερα, ωστόσο το ιστορικό της ήταν θετικό για πρόσφατη αναπνευστική λοίμωξη, η οποία θεραπεύτηκε με αμοξικιλλίνη/κλαβουλανικό οξύ, ιβουπροφαίνη και ακεταμινοφαίνη. Η κλινική εικόνα σε συνδυασμό με τους αυξημένους δείκτες φλεγμονής έθεσαν ισχυρή υποψία σοβαρής στρεπτοκοκκικής νόσου οδηγώντας στην εισαγωγή της ασθενούς και στη χορήγηση κλινδαμυκίνης. Κατά τη διάρκεια της νοσηλείας έγινε πλήρης έλεγχος για λοιμώδη και ρευματικά νοσήματα, ενώ η κλινδαμυκίνη διακόπηκε λόγω διάρροιας. Στο σημείο αυτό, ο αρνητικός διαγνωστικός έλεγχος σε συνδυασμό με την έλλειψη ανταπόκρισης στην εμπειρική αντιβιοτική αγωγή με κλινδαμυκίνη έθεσαν την υποψία ανοσολογικής αντίδρασης. Τελικά, η ασθενής διαγνώστηκε με αντίδραση δίκην ορονοσίας και θεραπεύτηκε επιτυχώς με κορτικοστεροειδή.

Η αντίδραση δίκην ορονοσίας πρέπει να λαμβάνεται υπόψιν σε ασθενείς με εμπύρετο εξάνθημα στα πλαίσια πρόσφατης λοίμωξης ή/και λήψης αντιβιοτικής αγωγής. Το περιστατικό αυτό τονίζει τη σημασία της κλινικής διάγνωσης σε ασθενείς με αντίδραση δίκην ορονοσίας. Επιπλέον, αναδεικνύεται η αναγκαιότητα εκλογικευμένης χρήσης απλών διαγνωστικών εξετάσεων, όπως το RST. Η κατάχρηση τους μπορεί να οδηγήσει σε ψευδώς θετικά αποτελέσματα περιπλέκοντας την διαχείριση των περιστατικών με περιττές αντιβιοτικές αγωγές και νοσηλείες.

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FIGURES AND TABLES.

Figure 1. The Diffuse Maculopapular Rash of the Patient.

Legend: The diffuse maculopapular pattern of the developed rash; note the occasional urticarial-like plaques in the area of arms (A) and legs (B).

322 ***Table 1.*** The parameters of the Centor score.

323

Fever (more than 38 °C)	+1
Anterior cervical lymphadenopathy	+1
Tonsillar exudate	+1
Lack of cough	+1
Age 3-14 years	+1
Age 15-44 years	0
Age >44 years	-1

324

325 Legend: The calculation of the Centor score is the first step in the clinical evaluation of pharyngitis.
326 Patients with a Centor score of 3 or more should be tested with a RST. A positive result is an
327 indication for antibiotic treatment, but a negative result should be investigated with a throat culture.
328