Journal of Clinical & Experimental Dermatology Research

Schryver et al., J Clin Exp Dermatol Res 2015, 6:3
DOI: 10.4172/2155-9554.1000279

Case Report Open Access

Severe Serum Sickness-Like Reaction: Challenges in Diagnosis and Management

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Received date: Mar 24, 2015, **Accepted date:** Apr 28, 2015, **Published date:** Apr 04, 2015

Abstract

We report a case of serum sickness-like reaction (SSLR) in a 15-month-old boy following oral amoxicillin therapy for an acute otitis media. While symptoms of SSLR improved with a non-steroidal anti-inflammatory (NSAID) and oral corticosteroids, he developed a duodenal ulcer. A nasopharyngeal PCR was positive for Influenza A virus during active disease. A graded challenge to amoxicillin conducted subsequently was negative. It is important to consider infectious causes for SSLR and incorporate proton pump inhibitors if NSAIDs and corticosteroids are used simultaneously to prevent gastric complications. Graded oral challenge to the suspected culprit medication proved to be safe in this case and future large scale studies exploring its role in establishing drug related SSLR in patients are required.

Keywords Serum-sickness; Serum sickness like; Children; Amoxicillin

Case Report

A 15 month-old, previous healthy, non-atopic boy presented to the emergency department of the Montreal's Children Hospital with fever, urticarial plaques and swollen joints, 8 days after initiating treatment with oral amoxicillin for acute otitis media. On clinical examination he appeared generally well with no signs of distress. Skin examination revealed widespread confluent annular and polycyclic urticarial plaques, some with dusky to purpuric centers (Figure 1). No mucosal involvement neither lymphadenopathy was noted. Pulmonary and cardiac examination was unremarkable. Patient had noticeable swelling of the hands and ankles. Laboratory investigation revealed normal complete blood count and renal function and mildly elevated inflammatory parameters (sedimentation rate of 11 mm/h, C-reactive protein 10.55 mg/L). Based on clinical manifestation, the diagnosis of serum sickness-like reaction (SSLR) was made with amoxicillin suspected as the most likely trigger and treatment with an oral non-steroidal anti-inflammatory drug (NSAID) and anti-histamine first generation (naproxen 5 mg/kg/dose and Benadryl 1 mg/kg/dose) was prescribed. The following day, patient returned to the emergency room with fever as well as worsening joint and cutaneous symptoms. Oral prednisone (1 mg/kg/day) was initiated and naproxen was discontinued. On the next day, while SSLR symptoms had improved, the patient was admitted to the hospital with anorexia, melena and anemia. Gastroscopy was performed and revealed a bleeding duodenal ulcer. Oral corticosteroids were subsequently discontinued and patient was treated with oral antihistamines and a proton pomp inhibitor (PPI, esomeprazole). His symptoms resolved over few days and he was discharged one week later in good general condition. A nasopharyngeal aspirate was sent for PCR during patient's hospital stay and was positive for Influenza A virus. Two months after hospital discharge, the patient underwent a graded oral challenge to amoxicillin (60 mg initially followed by 540 mg 20 minutes later). No reaction occurred within two weeks following the challenge.

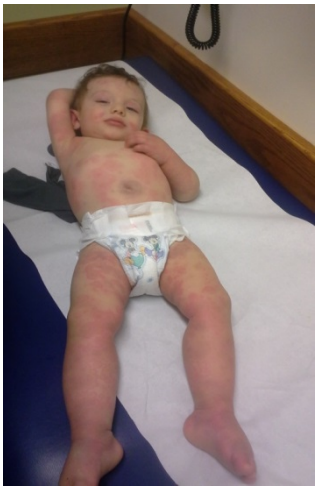

Figure1: On examination, he had widespread pruritic annular and polycyclic urticarial plaques. The rash was pruritic and lesions were migratory with central clearing.

Discussion

It is important to distinguish the more common serum sickness-like reaction (SSLR) from true serum sickness [1,2]. Serum sickness is a systemic immunological disorder, considered a type III immune complex disease induced by the deposition of circulating immune complex in blood vessels and other tissues, complement activation and the subsequent inflammatory response. This is most frequently

induced by administration of foreign proteins such as antithymocyte globulin or horse serum. True serum sickness is very rare.

Similarly to serum sickness, SSLR is characterized by fever, rash and joint involvement usually developing within 1-2 weeks following culprit medication or a trigger of other nature. However, renal and hepatic involvement is rare. The most frequent cutaneous findings include macular exanthem, urticarial eruption which may have dusky to purple centers, and eruption mimicking erythema multiforme. The other primary clinical feature is joint involvement manifesting with arthralgia and swelling. The hallmark of SSLR is its benign outcome [1,2]. The pathogenesis is not known but is not associated with circulating immune complexes, hypocomplementemia or vasculitis [2,3]. SSLR has been described in association with a variety of non-protein drugs (particularly antibiotics), viral and bacterial infections and vaccines [3,4]. Both viral and bacterial infections are known etiologic factors of urticaria in children but no studies have been published evaluating the role of infectious etiologies for SSLRs.

The most common cause of SSLR is thought to be Cefaclor [4]. Penicillin related SSLR is rare, with a report incidence of 0.007-0.004% but studies suggest that the diagnosis is probably under recognized [5-7]. Viral and bacterial infections were also implicated in the pathogenesis of SSLR [3].

The diagnosis in this particular case was made clinically based on the typical symptoms of fever, rash and joint swelling, as seen in SSLR. The differential diagnosis included urticarial viral exanthem, however prominent joint symptoms and absence of mucosal involvement favored against it.

A limitation in this clinical case is that neither complement (C3, C4, CH50) nor circulating immune complexes levels were measured. Although these are important markers for differentiating SSLR from true serum sickness, we believe the diagnosis of true serum sickness is very unlikely given the typical clinical characteristics in the absence of organ failure.

Retrospectively, the most likely trigger in this case was a viral infection rather than amoxicillin given the negative challenge and the positive PCR for influenza A. However, it is also possible that similarly to common maculopapular exanthem seen following amoxicillin administration during acute mononucleosis, clinical manifestation resulted from an interaction between the virus and amoxicillin [8,9]. In cases of SSLR without internal organ involvement where causal relationship with a concomitantly taken medication is doubtful, a closely supervised oral challenge may be useful. In our patient, the oral provocation test with amoxicillin was negative ruling out an immune mediated allergic reaction solely triggered by amoxicillin. SSLR is most common in children and infection, with or without antibacterial agent, precedes the onset of symptoms in most cases [10].

Because SSLR can result from both infection and medication, establishing the cause may be difficult. Ponvert et al. documented the safety of an oral challenge with a beta lactam antibiotic in a subset of children with SSLR to a beta lactam and estimated the positive rate to be 36.4% [3] suggesting that most cases are not drug related. However, their study needs to be replicated at a larger scale before definitive conclusions are derived.

There are no evidence based guidelines or controlled trials regarding the optimal treatment of SSLR. Current therapy is based on case reports and retrospective medical record views and consists mainly on antihistamines, NSAIDs and in more severe cases, short courses of systemic corticosteroids [2,5]. However, the lack of established benefit of these treatments should be weighed against their potential side effects. All NSAID regimens increased upper gastrointestinal complications (mainly naproxen 4·22, (95% CI, 2·71, 6·56) [11]. These complications may occur within the first week of treatment [12]. In a recent meta-analysis it was reported that adding a proton pump inhibitor (but not a histamine-2 receptor antagonist) to treatment with NSAIDs will reduce the risk of symptomatic ulcers associated with NSAIDs treatment [13].

In contrast short courses (less than 2 weeks) of synthetic corticosteroids (mainly prednisone, prednisolone and betamethazone) that have a more potent anti-inflammatory activity compared to cortisol, a reduced mineralocorticoid effect and a longer biological half-life, were not associated with gastric ulcer, or suppression of the adrenal function [14]. However, given previous reports on increased risk of gastrointestinal complications with the use of both medications [15] it is likely, that the use of both had contributed to the development of his duodenal ulcer. Our case demonstrated the need to add a proton pump inhibitor in children treated simultaneously with NSAIDS and systemic steroids to prevent gastrointestinal complications, even for relatively short treatment intervals.

Conclusion

We report a case of most likely severe virally triggered SSLR complicated by a duodenal ulcer following combined therapy with NSAIDs and corticosteroids. Oral challenges with the culprit agent should be considered to establish final diagnosis and further management. If management strategy includes both NSAIDS and/or steroids, physicians should consider adding a proton pump inhibitor for gastric protection. Future studies are needed to investigate the role of oral challenges in a large sample of patients presenting with suspected drug-induced SSLR.

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