BRIEF ARTICLE

True Serum Sickness, Pearls for Clinical Diagnosis

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ABSTRACT

Background: True serum sickness is a type 3 hypersensitivity reaction against foreign antibodies, resulting in vasculitis and an acute clinical presentation. Historically reported with anti-venin, currently anti-thymocyte globulin in the context of transplant rejection prophylaxis remains one of the most common causes. The classic clinical triad of fevers, arthralgias, and rash is not consistently present, and the rash is often difficult to distinguish from typical drug reactions. However, certain unique findings can assist with diagnosis.

Case Presentation: We present a case of true serum sickness secondary to anti-thymocyte globulin featuring key exam and laboratory findings that enabled differentiation from other possible overlapping clinical entities, particularly drug reactions.

Conclusions: Marked temporomandibular jaw pain is an important early clue to the diagnosis. Linear serpiginous erythema along the plantar margin may be a specific feature when rash is present. To our knowledge, neither have been reported in similar clinical entities including serum-sickness-like reaction. Serum complement levels and direct immunofluorescence (if skin biopsy done) are useful for distinguishing true serum sickness from primary differentials serum sickness-like reaction and drug rash with eosinophilia and systemic symptoms.

CASE PRESENTATION

A 28 year-old woman with type 1 diabetes and penicillin allergy was admitted for pancreatic transplant, complicated by graft failure on day 2 requiring graft pancreatectomy. She received 2 doses of anti-thymocyte globulin (ATG) on day of transplant and briefly mycophenolate and tacrolimus. She was discharged on trimethoprim-sulfamethoxazole, linezolid, ciprofloxacin, metronidazole, fluconazole, and valacyclovir. Nine days later she was readmitted for spiking fevers to 102.2F and severe myalgias and arthralgias rendering her nearly immobile. She had marked bilateral temporomandibular joint (TMJ) pain that limited her speech and intake. Intravenous antibiotics were initiated and a rash developed shortly after. Examination was notable for a diffuse morbilliform exanthem featuring unusual serpiginous bands of erythema on the lateral aspects of the bilateral feet occurring at the margin of plantar skin (Figure 1). Her face was edematous. Joint swelling and lymphadenopathy were difficult to evaluate due to habitus. Infectious workup, blood counts, metabolic panel, creatinine kinase, and urinalysis were notable for elevated transminases that had been downtrending since her previous admission, and neutrophilia (Table 1). Skin biopsy showed mild vacuolar interface dermatitis. Further labs revealed low CH50, C3, and C4 (Table

1). A diagnosis of true serum sickness (SS) secondary to ATG was rendered. Prednisone taper was initiated, and on follow-up 3 weeks later her symptoms had resolved.

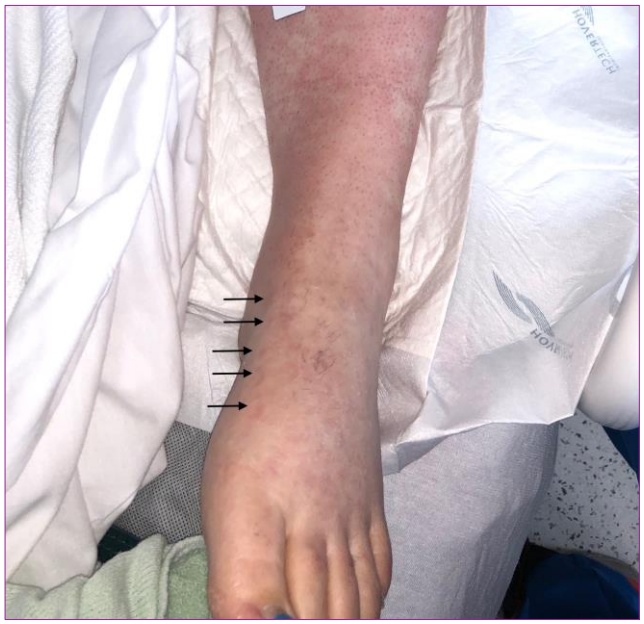

Figure 1. Clinical image demonstrating serpiginous bands of erythema along the plantar margin.

DISCUSSION

ATG persists as one of the most common causes of SS given its continued popularity in transplant rejection prophylaxis, and immunogenicity as a heterologous antibody derived from rabbits or horses. In a prospective cohort study of 240 renal transplant patients receiving ATG, 7.5% developed SS.[1] The pathomechanism involves a type 3 hypersensitivity with deposition of circulating antibody complexes, triggering complement consumption and vasculitis. This vasculitis produces the classic clinical triad of spiking fevers, debilitating musculoskeletal pain, and rash. An urticarial rash is classic, however morbilliform presentations are common.

Onset from exposure is 7-14 days, corresponding to time required to mount an antibody response. Facial swelling, lymphadenopathy, and nephritis are additional common features.

This pathomechanism is similar to how disease manifests in certain autoimmune conditions, such as nephritis in systemic lupus erythematosus. Conceivably, autoimmune conditions such as in our patient may reflect a greater tendency to develop SS, and the literature is limited but suggestive. A retrospective study of reports of rituximab-induced SS in the French Pharmacovigilance Database found a higher incidence in patients being treated for autoimmune diseases (6.4 cases/10^5 doses) compared to those treated for hematologic malignancies (0.5 cases/10^5 doses), especially for lupus (48.6 cases/10^5 doses).[2] Interestingly, in a phase II clinical trial of 58 patients receiving ATG for treatment of type 1 diabetes, all patients localized to the treatment arm (38) developed SS.[3]

Characteristic clinical findings in ATG-related SS and possibly SS in general include TMJ pain as an early clue, and serpiginous bands of erythema along the palmar or plantar margins. In studies detailing localization of arthralgias, 5 of 5 ATG-induced cases and 3 of 8 infliximab-induced cases reported jaw pain.[4-6] In studies describing rashes in detail (all ATG), palmoplantar bands were present in 29 of 39 (74%) patients.[7,8]

SS remains a clinical diagnosis and biopsies are generally not indicated, however transplant patients are exposed to multiple new medications and susceptible to many infections. Thus, skin biopsies can be helpful to navigate a broadly overlapping differential.

Table 1. Key laboratory investigations at time of admission

Complete Blood Count	Value	Reference Range
White blood cells	15.99 k/uL	4.00 – 11.00 k/uL
Neutrophils, absolute	15.17 k/uL	1.80 – 8.00 k/uL
Lymphocytes, absolute	0.27 k/uL	1.00 – 5.00 k/uL
Eosinophils, absolute	0.14 k/uL	0.00 – 0.60 k/uL
Hemoglobin	9.7 g/dL	12.0 – 16.0 g/dL
Platelets	217 k/uL	150 – 450 k/uL
Metabolic Panel		
Blood urea nitrogen	21 mmol/L	22 – 29 mmol/L
Creatinine	0.7 mg/dL	0.7 – 1.1 mg/dL
Glucose	166 mg/dL	74 – 99 mg/dL
Albumin	3.8 g/dL	3.2 – 5.2 g/dL
Total Bilirubin	0.6 mg/dL	0.3-1.2 mg/dL
Alkaline phosphatase	122 U/L	40 – 150 U/L
Aspartate aminotransferase	41 U/L	<35 U/L
Alanine aminotransferase	76 U/L	<55 U/L
Inflammatory Panel		
Creatinine Kinase	32 U/L	30-170 U/L
C-Reactive Protein	21.7 mg/dL	<0.5 mg/dL
Erythrocyte Sedimentation Rate	69 mm/h	0 – 30 mm/h
CH50 Complement	35 U/mL	42 – 95 U/mL
C3 Complement	77 mg/dL	83 – 193 mg/dL
C4 Complement	11 mg/dL	15 – 57 mg/dL
Anti-nuclear antibody	Negative	Negative
Rheumatoid Factor	14.1 IU/mL	<30.0 IU/mL
CCP IgG Antibody	1.5 U/mL	<3.0 U/mL
Infectious Panel		
Blood culture (x3)	No growth	No growth
*Gastrointestinal pathogens PCR panel**	None detected	None detected
*Respiratory pathogens PCR panel**	None detected	None detected
*Urinalysis**	All normal	All normal
Urine culture	No growth	No growth
COVID-19 swab PCR	None detected	None detected
Cytomegalovirus viral load	None detected	None detected
Epstein-Barr virus viral load	None detected	None detected
Human Herpesvirus-6 PCR	None detected	None detected

*Gastrointestinal panel genera: Campylobacter, Plesiomonas, Salmonella, Vibrio, Yersinia, E. coli, Shigella, Cryptosporidium, Cyclospora, Entamoeba, Giardia, Adenovirus, Astrovirus, Norovirus, Rotavirus, Sapovirus.

Respiratory panel genera; Adenovirus, Coronavirus, Metapneumovirus, Rhinovirus, Influenza, Parainfluenza, RSV, Mycoplasma, Chlamydia.

Urinalysis: Glucose, protein, bilirubin, urobilinogen, pH, blood, ketone, nitrite, leukocyte esterase, opacity, color.

Despite the proposed pathomechanism, skin biopsies rarely show the specific finding of vasculitis. Out of 18 collective skin biopsies reported in the literature (all ATG), only one featured vasculitis.[7,8] However, of 14 tissue samples that were also sent for direct immunofluorescence (DIF), 10 (71%) showed immune deposits within blood vessels with varying combinations of IgA/M/E and C3, but not IgG.[7,8] Hence if a biopsy is being considered with SS on the

differential, particularly ATG-related, an accompanying DIF is recommended.

Serum sickness-like reaction (SSLR) is distinct from SS but often confused with the latter due to overlapping clinical features and timing of onset. Rather than an immune response against foreign antibodies, SSLR is a drug reaction, often from antibiotic or antiepileptic exposure in pediatric patients. The exact pathomechanism is unknown, however immune complexes and vasculitis are absent, therefore hypocomplementemia and nephritis do not occur. Also, to our knowledge, jaw pain and serpinginous bands along the volar margins have not been reported in SSLR. Both SS and SSLR are self-limited once the causative agent is discontinued. In general there are no long-term sequelae. Systemic steroids are sometimes indicated if severely symptomatic.

A more serious entity with substantial clinical overlap is drug rash with eosinophilia and systemic symptoms (DRESS), a morbilliform drug eruption with the key feature of end-organ damage, most commonly of the kidneys and liver. Eosinophilia is characteristic but often absent. Fever, arthralgias, and lymphadenopathy are common, and facial edema is an important early clue. Like SS, skin biopsies tend to be nonspecific. Both entities can feature nephritis, leading to similar findings on urinalysis and renal function tests. In our patient, the distinguishing features were hypocomplementemia, impressive TMJ pain, and peculiar serpiginous bands occurring at her plantar margins.

We propose complement levels as an accessible and effective test in ruling out overlapping entities, including SSLR and DRESS. C1q binding and Raji cell assays for detecting immune complexes can be helpful, however these are not widely available. An ELISA for anti-ATG with 86% sensitivity, despite being a major diagnostic criterion for SS, suffers from significant interlaboratory variability and limited availability.[9]

Hypocomplementemia is currently only a minor diagnostic criterion for SS, as levels do not precisely parallel clinical symptoms. However, earlier checks could be more helpful. On review of the literature, complement levels collectively obtained in 39 patients with ATG-related SS showed 31 were low in either C3 or C4 (79%).[1,4,5,8,10] The 8 cases with normal complement were drawn later (18-25 days after first ATG dose) compared to cases with low complement (7-14 days), suggesting higher sensitivity when checked earlier. The largest prospective study followed 11 patients and found complement levels reached their nadir an average of 11 days after starting ATG.[8] Compared with symptom onset averaging 9.5 days, this suggests complement levels are more useful when drawn closer to symptom onset. Some patients had low complement at baseline, however onset of SS led to even further decreases.[8] Complement levels were also low in 3 of 3 rituximab-induced cases, checked at symptom onset 7-9 days after last infusion.[11,12]

CONCLUSION

In summary, we present a case of SS presenting with lesser-known but characteristic exam features of marked TMJ pain (early clue), and serpiginous bands along the plantar margin. We recommend checking complement levels, ideally close to symptom onset, as a quick and effective method to distinguish from primary differentials SSLR and DRESS. If skin

biopsy is done, we recommend including DIF.

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