



Concurrence of Fatal Staphylococcal Toxic Shock Syndrome and Systemic Lupus Erythematosus

Shiue-Wei Lai¹, Kuo-Ming Yeh², Feng-Cheng Liu³, Jung-Chung Lin², Fu-Chiang Yeh³, Sheng-Kang Chiu²

¹Departments of Internal Medicine, Division of Hematology and Oncology, ²Division of Infectious Diseases and Tropical Medicine, ³Division of Rheumatology, Immunology and Allergy, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, Republic of China

Staphylococcal toxic shock syndrome (STSS) is an acute, toxin-mediated febrile illness that rapidly leads to multiple organ dysfunction syndromes, and systemic lupus erythematosus (SLE) is a multisystem autoimmune and inflammatory disease. Differential diagnosis in STSS involved a number of common diseases associated with a wide range of nonmenstrual-related conditions, including SLE. Therefore, it is difficult to distinguish from each other initially. We report a case of concurrent fatal STSS and SLE who was treated as sepsis initially, which leads to grave prognosis.

Key words: *Staphylococcus aureus*, systemic lupus erythematosus, toxic shock syndrome

INTRODUCTION

Toxic shock syndrome (TSS) is a toxin-mediated acute life-threatening illness, usually precipitated by infection with either *Staphylococcus aureus* (*S. aureus*) or group A *Streptococcus*. It is characterized by fever, myalgias, sore throat, edema, scarlatiniform rash, and desquamation.¹ Although classically associated with tampon use,¹ TSS has also been associated with various nonmenstrual-related conditions. SLE is a multisystem autoimmune disease characterized by a myriad of autoantibody production. The diagnosis of SLE is based on a combination of clinical findings and laboratory evidence. Although the diagnosis is based on the exclusion of infection, viral or bacterial pathogens may serve as an environmental trigger for the development or exacerbation of SLE in the genetically predetermined individual. The case represents an interesting concurrence of TSS with coincidental SLE.

CASE REPORT

A 45-year-old woman presented to the emergency department with a 3-day history of fever, drowsy consciousness,

tachypnea, skin rash, and generalized jaundice. She denied any previous medical history. On admission, her presenting vital signs were: A temperature of 39.2°C, a pulse of 172 beats/min, a respiratory rate of 28 breaths/min and blood pressure of 60/42 mmHg. Physical examinations revealed E₃V₂M₆ in Glasgow Coma Scale initially. The pupils were sluggishly reactive to light, and the conjunctivae were pale. Icteric sclera and oral ulcer were noted. There were bilateral rhonchi, coarse crackles and irregular cardiac rhythm without murmurs. Multiple nonblanchable violaceous rash with desquamation was observed on her face and distal extremities [Figure 1a].

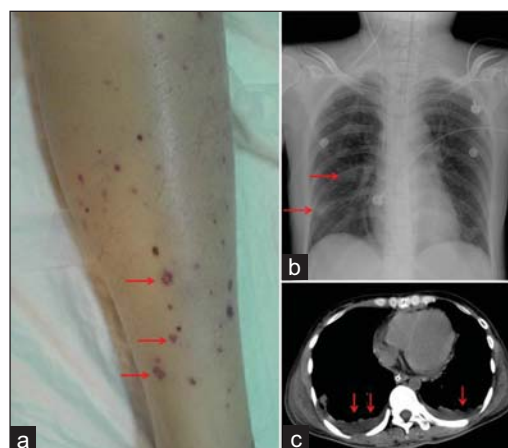


Figure 1. (a) Multiple nonblanchable violaceous rash with desquamation was observed over distal extremities (red arrows). (b) Chest radiography showing small nodular and mass-like opacities at the right upper, middle, and bilateral lower lung fields associated with infiltrations in both lung fields (red arrows). (c) Noncontrast enhanced computed tomography of abdomen showing patch opacities in bilateral lower lung zones and few pleural effusions (red arrows)

Received: September 6, 2013; Revised: April 21, 2014;
Accepted: April 29, 2014

Corresponding Author: Dr. Sheng-Kang Chiu, Division of Infectious Diseases and Tropical Medicine, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, No. 325, Section 2, Cheng-Kung Road, Neihu 114, Taipei, Taiwan, Republic of China. Tel: +886-2-87923311. E-mail: skchiu@mail.ndmctsgh.edu.tw

No joints swelling were found. The extremities were cool, with 1+ pulses in the arms and legs. The remainder of the examination was normal.

The complete blood count disclosed as following: Total white blood cell count: 3400/ μ L (normal: 4500-11,000/ μ L), hemoglobin 14.3 g/dL (normal women: 11.3-15.3 g/dL), platelet count 27,000/ μ L (normal: 150,000-400,000/ μ L). The laboratory data revealed elevation of aspartate transaminase 1019 U/L (normal: 10-40 U/L), alanine transaminase 235 U/L (normal: 10-55 U/L), total bilirubin 7.2 mg/dL (normal: 0.0-1.0 mg/dL), direct bilirubin 5.3 mg/dL (normal: 0.0-0.4 mg/dL), creatine kinase 1489 U/L (normal: 60-400 U/L), positive at 1:640 dilutions of antinuclear antibodies (ANAs) in speckled pattern (normal: <1:40), complement 3 level 19.0 mg/dL (normal: 86-184 mg/dL) and complement 4 level 6.9 mg/dL (normal: 20-58 mg/dL). The urine specimen showed protein 3+, nitrite 2+, bacteria 2+, granular cast 2+, and cellular cast 1+.

The chest radiograph revealed small nodular opacities at the right upper, middle, and bilateral lower lung fields associated with infiltrations [Figure 1b]. The pleural effusion in both lung fields was found by the computed tomography of the abdomen [Figure 1c]. The patient was intubated and received the administration of vancomycin (1000 mg every

24 h), imipenem-cilastatin sodium (500 mg every 8 h), vasopressor (norepinephrine, 26 μ g/min and dopamine, 30 μ g/kg/min) and glucocorticoids (hydrocortisone 50 mg every 6 h). Despite aggressive intensive care with continuous veno-venous hemofiltration, she succumbed to the profound sepsis the next day.

The results of blood culture, sputum culture and urine culture demonstrated methicillin-susceptible *S. aureus* (MSSA) growth, and negative findings were noted in influenza A and B antigen screen, pneumocystis jiroveci pneumonia and cytomegalovirus by molecular analysis of polymerase chain reaction products, human immunodeficiency virus, herpes simplex virus, Epstein-Barr virus, rapid plasma reagin, hepatitis C virus antibody, hepatitis B virus surface antigen, sputum chlamydia antigen, the serum mycoplasma antibody, nasopharynx swab, rectal swab, leptospirosis using Enzyme-Linked Immunosorbent Assay and the Weil-Felix test.

DISCUSSION

Toxic shock syndrome associated with *S. aureus* was first described in a series of pediatric cases in 1978 by Todd *et al.*¹ and is characterized by the features shown in Table 1.^{2,3} Approximately, one-half of reported TSS cases

Table 1. Case definition and clinical characteristics of the patient

CDC ^a case definition of STSS ^b	Patient	ACR ^c criteria of SLE ^d	Patient
Fever	39.2°C	Malar rash	No
Hypotension	SBP ^e : 60 mmHg	Photosensitivity	No
Rash	Macules on the face and distal limbs	Discoid rash	No
Desquamation	Palms and soles	Serositis	Pleuritis
Multisystem involvement		Arthritis	No
Gastrointestinal	No	Oral ulcers	Yes
Muscular	CK ^f : 1489 U/L	Persistent proteinuria	3+ urine protein on dipstick
Mucous membranes	Oropharyngeal hyperemia	Hemolytic anemia	Platelet: 27,000/ μ L
Renal	No	Seizures or psychosis	No
Hepatic	Total bilirubin: 7.2 mg/dl Direct bilirubin: 5.3 mg/dl AST ^g : 1019 U/L ALT ^h : 235 U/L	ANA ^k Positive APLA ^l or anti-ds-DNA ^m or anti-Sm ⁿ	1:640 dilutions with speckled pattern No
Hematologic	Platelet: 27,000/ μ L		
Central nervous system	No		
Negative results on the following tests, if obtained	Yes		
Blood, throat, or CSF ⁱ cultures for another pathogen			
Serologic tests for RMSF ^j , leptospirosis, or measles			

Bold black means positive results. ^aCDC = centers for diseases control; ^bSTSS = staphylococcal toxic shock syndrome; ^cACR = american college of rheumatology; ^dSLE = systemic lupus erythematosus; ^eSBP = systolic blood pressure; ^fCK = creatine kinase; ^gAST = aspartate aminotransferase; ^hALT = alanine aminotransferase; ⁱCSF = cerebrospinal fluid; ^jRMSF = rocky mountain spotted fever; ^kANA = antiphospholipid antibody; ^lAPLA = antiphospholipid antibodies; ^mAnti-ds-DNA = anti-double-stranded deoxyribonucleic acid antibodies; ⁿAnti-Sm = anti-smooth muscle antibodies

are nonmenstrual.⁴ Nonmenstrual TSS has been seen in a variety of clinical situations, such as respiratory infections following influenza, and enterocolitis.⁵ The case-fatality rate for nonmenstrual TSS was around 5%.⁶ In contrast to the menstrual cases, this rate did not decrease over time.

Systemic lupus erythematosus is a protean autoimmune disease where autoantibodies are frequently targeted against intracellular antigens of the cell nucleus. Updated American College of Rheumatology (ACR) criteria for the diagnosis of SLE include several autoantibodies.⁷ SLE is likely if 4 of 11 criteria are met over any time period as shown in Table 1. A case of fatal staphylococcal toxic shock syndrome (STSS) in a patient with SLE is rarely reported previously, perhaps such patients are often treated empirically with antibiotics at the earliest sign of sepsis. There are several overlapping diagnostic criteria between SLE and STSS and the typical skin rash in STSS might be modified by immunodeficiency state. As a result, it is difficult to distinguish from these two diseases at first.

The patient's illness met the criteria for STSS as shown in Table 1 and poor treatment response was found, including vancomycin, imipenem-cilastatin sodium, and aggressive resuscitation. Acute deteriorated clinical course suggested possible immunodeficiency problem and SLE was diagnosed by the ACR criteria.⁷ However, the other autoimmune profiles and the studies of immunoglobulins were unavailable because of the 1-day hospital course. In addition, the amount of pleural effusion was inadequate for thoracentesis at that time.

Immunodeficiency may involve in the vulnerability of SLE patients to infections and infections may mimic exacerbations of SLE. It is sometimes difficult to choose antibiotics or immunosuppressive therapy in SLE patients with infectious presentation. Despite increased awareness of SLE and multiple newly developed antibiotics, sepsis is still responsible for 30-40% of morbidity and mortality rate in SLE patients.⁸

By definition, STSS is caused by the species whether methicillin-resistant *S. aureus* (MRSA) or MSSA which produces the toxins, including toxic shock syndrome toxin-1 and enterotoxins A through E which act together as superantigens that stimulate the release of various cytokines, prostaglandins, and leukotrienes, which induce the signs and symptoms.⁹ Microbial superantigens exhibit environmental factors that may trigger autoimmune disease in genetically susceptible host.¹⁰ Friedman *et al.* showed that microbial superantigens may trigger the development of autoantibodies characteristic of SLE.¹¹ It is possible that STSS presents as the initial presentation in SLE due to microbial superantigens in the pathogenesis of systemic autoimmune disease. Although MRSA may be more virulent than MSSA,¹² some case reports demonstrated MSSA can induce devastating clinical courses.¹³⁻¹⁵

Additionally, patients with SLE could present as thrombotic thrombocytopenia purpura (TTP) rarely which was characterized by the clinical pentad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, renal dysfunction, fever, and neurologic abnormalities.¹⁶ It might be challenging to diagnose early because both disorders share many overlapping clinical features.¹⁷ However, MAHA in TTP and SLE may be distinguished by the presence of schistocytes, which are mainly caused by mechanical trauma in the microvasculature. An immune-mediated hemolytic process occurs in SLE resulting from anti-RBC antibodies.¹⁸ In our case, the clinical findings of schistocytes, renal dysfunction, and neurologic abnormalities were not observed and the diagnosis of TTP was less suspected. In addition, Kwok *et al.* exhibited patients with SLE who are in the active stage or who have renal involvement have the increased risk for TTP, which was incompatible with our case.¹⁹

Antinuclear antibodies are common biomarkers for assessing the diagnosis of patients with autoimmunity and probably occur in other systemic diseases, including infectious diseases.²⁰ We usually consider ANA titer of 1:160 as decision-making levels and there were limited information about false positive result of ANA in a patient with STSS.²¹ Our patient had strongly positive ANA titer of 1:640 in speckled pattern which was more likely truly positive rather than false positive in our opinion.

Supportive therapy with reversal of hypotension is the mainstay of therapy for STSS. Patients with STSS typically received intravenous clindamycin 600 mg every 8 h plus oxacillin or nafcillin 2000 mg every 4 h.²² Vancomycin was suggested for patients with risk factors for MRSA infection or colonization. Clindamycin is advocated because, as protein synthesis inhibitor; it reduces toxin synthesis *in vitro*. A semisynthetic penicillin is suggested to eliminate potential focus of infection as well as to eradicate persistent carriage that might increase the likelihood of recurrent illness.⁸ In addition, intravenous immunoglobulins may be considered to improve the prognosis if SLE is suspected by the clinical criteria with concomitant infection and methylprednisolone or plasma exchange could be used for SLE patients whose disease flare up.²³ Among the reported cases of TSS with SLE [Table 2], the patients, recovered well post adequate antibiotics use and supportive care.²⁴⁻²⁶ It was important that the reported cases all had a history of SLE first and experienced TSS thereafter. Clinically, such patients were often searched for medical aid when clinical symptoms developed and were treated vigorously with antibiotics at the earliest sign of infection. Our case underwent the medical examination 3 days after pyrexia and was treated with vancomycin and imipenem-cilastatin

Table 2. The cases of toxic shock syndrome with systemic lupus erythematosus

References	Patient	Tampon use	ANA [#]	Pattern	Antibiotics	Pathogen	Disease resolved post admission	Alive
22	23 ^{##} /Female	Yes	N/A**	N/A	Cephalothin	<i>Staphylococcus aureus</i>	6 days	Yes
23	38/Female	No, but IUD***	1:640	Speckled	Cloxacillin Gentamicin Clindamycin	Not detected	12 days	Yes
24	50/Female	N/A	N/A	N/A	N/A	<i>Staphylococcus aureus</i>	5 weeks	Yes
Our case	45/Female	No	1:640	Speckled	Vancomycin Imipenem	<i>Staphylococcus aureus</i>		No

[#]ANA = antinuclear antibodies; ^{##}Age = years old; ^{**}N/A = not applicable; ^{***}IUD = intrauterine device

sodium empirically which may be not the suggested combination therapy for STSS because of delayed diagnosis, including STSS and SLE. That is may be the main cause of treatment failure.

CONCLUSION

It is often encountered to distinguish between a lupus flare-up and an acute infection. Early recognition and proper treatment are essential to alleviate the mortality. The potential mechanisms of microbial superantigens in the pathogenesis of lupus and the usefulness of combined antibiotic therapy with immunosuppressive agents for SLE patients with STSS remain to be evaluated.

DISCLOSURE

The authors declare this study has no conflict of interest.

REFERENCES

- Todd J, Fishaut M, Kapral F, Welch T. Toxic-shock syndrome associated with phage-group-I *Staphylococci*. *Lancet* 1978;2:1116-8.
- Wharton M, Chorba TL, Vogt RL, Morse DL, Buehler JW. Case definitions for public health surveillance. *MMWR Recomm Rep* 1990;39:1-43.
- Case definitions for infectious conditions under public health surveillance. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 1997;46:1-55.
- Centers for Disease Control (CDC). Reduced incidence of menstrual toxic-shock syndrome – United States, 1980-1990. *MMWR Morb Mortal Wkly Rep* 1990;39:421-3.
- Reingold AL, Hargrett NT, Dan BB, Shands KN, Strickland BY, Broome CV. Nonmenstrual toxic shock syndrome: A review of 130 cases. *Ann Intern Med* 1982;96:871-4.
- Hajjeh RA, Reingold A, Weil A, Shutt K, Schuchat A, Perkins BA. Toxic shock syndrome in the United States: Surveillance update, 1979-1996. *Emerg Infect Dis* 1999;5:807-10.
- Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
- Doria A, Canova M, Tonon M, Zen M, Rampudda E, Bassi N, *et al.* Infections as triggers and complications of systemic lupus erythematosus. *Autoimmun Rev* 2008;8:24-8.
- Parsonnet J. Mediators in the pathogenesis of toxic shock syndrome: Overview. *Rev Infect Dis* 1989;11 Suppl 1:S263-9.
- Tumang JR, Cherniack EP, Gietl DM, Cole BC, Russo C, Crow MK, *et al.* T helper cell-dependent, microbial superantigen-induced murine B cell activation: Polyclonal and antigen-specific antibody responses. *J Immunol* 1991;147:432-8.
- Friedman SM, Posnett DN, Tumang JR, Cole BC, Crow MK. A potential role for microbial superantigens in the pathogenesis of systemic autoimmune disease. *Arthritis Rheum* 1991;34:468-80.
- Rozgonyi F, Kocsis E, Kristóf K, Nagy K. Is MRSA more virulent than MSSA? *Clin Microbiol Infect* 2007;13:843-5.
- Lee YT, Chou TD, Peng MY, Chang FY. Rapidly progressive necrotizing fasciitis caused by *Staphylococcus aureus*. *J Microbiol Immunol Infect* 2005;38:361-4.
- Kotler DP, Sandkovsky U, Schlievert PM, Sordillo EM. Toxic shock-like syndrome associated with staphylococcal enterocolitis in an HIV-infected man. *Clin Infect Dis* 2007;44:e121-3.
- Akpaka PE, Monecke S, Swanston WH, Rao AC, Schulz R, Levett PN. Methicillin sensitive *Staphylococcus aureus* producing Pantone-Valentine leukocidin toxin in Trinidad & Tobago: A case report. *J Med Case Rep* 2011;5:157.
- Galbusera M, Noris M, Remuzzi G. Thrombotic thrombocytopenic purpura — then and now. *Semin Thromb Hemost* 2006;32:81-9.

17. Musio F, Bohen EM, Yuan CM, Welch PG. Review of thrombotic thrombocytopenic purpura in the setting of systemic lupus erythematosus. *Semin Arthritis Rheum* 1998;28:1-19.
18. George JN, Vesely SK, James JA. Overlapping features of thrombotic thrombocytopenic purpura and systemic lupus erythematosus. *South Med J* 2007;100:512-4.
19. Kwok SK, Ju JH, Cho CS, Kim HY, Park SH. Thrombotic thrombocytopenic purpura in systemic lupus erythematosus: Risk factors and clinical outcome: A single centre study. *Lupus* 2009;18:16-21.
20. Smeenk RJ. Antinuclear antibodies: Cause of disease or caused by disease? *Rheumatology (Oxford)* 2000;39:581-4.
21. Tozzoli R, Bizzaro N, Tonutti E, Villalta D, Bassetti D, Manoni F, *et al.* Guidelines for the laboratory use of autoantibody tests in the diagnosis and monitoring of autoimmune rheumatic diseases. *Am J Clin Pathol* 2002;117:316-24.
22. Herzer CM. Toxic shock syndrome: Broadening the differential diagnosis. *J Am Board Fam Pract* 2001;14:131-6.
23. D'Cruz DP, Khamashta MA, Hughes GR. Systemic lupus erythematosus. *Lancet* 2007;369:587-96.
24. Findlay RF, Odom RB. Toxic shock syndrome in a patient with systemic lupus erythematosus. *Int J Dermatol* 1982;21:140-1.
25. Chan RM, Graham HR, Birmingham CL. Toxic shock syndrome in a patient with systemic lupus erythematosus. *Can Med Assoc J* 1983;129:1201-2.
26. Huseyin TS, Maynard JP, Leach RD. Toxic shock syndrome in a patient with breast cancer and systemic lupus erythematosus. *Eur J Surg Oncol* 2001;27:330-1.