Right in Front of Our Eyes: Evolution of Streptococcal Toxic Shock Syndrome with Ischemic Optic Neuropathy

SALAHELDIN M. ELHAMAMSY, MD; MAZEN O. AL-QADI, MD; TARO MINAMI, MD; MARGUERITE NEILL, MD

ABSTRACT

INTRODUCTION: Toxic shock syndrome occurs from dysregulation of host inflammatory responses. Toxin-producing strains of Group A streptococcus cause TSS. Ischemic optic neuropathy rarely complicates septic shock. We present a rare case of streptococcal pharyngitis complicated by septic arthritis and TSS with reversible blindness due to non-arteritic ischemic optic neuropathy.

CASE: A 28-year-old man drove to our ED with exudative pharyngitis. A rapid streptococcal test was positive. While awaiting oral penicillin he became hypotensive refractory to IV fluids and developed knee effusion. The patient noted progressive dimming of his vision. Arthrocentesis yielded GAS. ICU course was complicated by ARDS but after 2 weeks the patient was weaned off vasopressors and the ventilator. He regained his vision and had no neurological sequelae. The patient's GAS isolate was M protein gene (emm) type 1 and T type 1. He was followed in the IM clinic for 9 months post discharge with complete resolution of symptoms.

CONCLUSION: The rapidity of the development of shock is attributed to streptococcal exotoxins acting as superantigens. GAS type M1 is commonly associated with severe shock in TSS. The severe shock was the likely cause of his ischemic optic neuropathy. Early recognition and aggressive management of TSS are crucial to clinical outcome.

KEYWORDS: Toxic shock syndrome, TSS, Staphylococcus aureus, Group A streptococcus

INTRODUCTION

Toxic shock syndrome (TSS) is a severe illness caused by dysregulation of host inflammatory responses resulting in multi-organ failure. Toxin-producing strains of *Staphylococcus aureus* (S. aureus) or Group A streptococcus (GAS) cause TSS. Streptococcal pharyngitis is almost never associated with TSS. Ischemic optic neuropathy rarely complicates septic shock, particularly in young individuals. We present a rare case of streptococcal pharyngitis complicated by septic arthritis and TSS with reversible blindness due to non-arteritic ischemic optic neuropathy.

CASE REPORT

A 28-year-old man drove himself to our emergency department with a 1-week history of fever and sore throat. On arrival to the emergency department, he was afebrile, normotensive, but had exudative pharyngitis. A rapid streptococcal antigen test was positive. Oral penicillin and intravenous fluids were administered. While awaiting for discharge (within 2 hours of initial triage), left knee pain developed and he became hypotensive. Over 3 hours, effusion developed in the other knee as did refractory hypotension. This was followed by progressive dimming of his vision to complete blindness. Vancomycin, piperacillin-tazobactam and clindamycin were given for toxic shock syndrome. A central venous catheter was inserted; vasopressors were started and the patient was admitted to the intensive care unit (ICU). An MRI of the brain was performed to evaluate his blindness, which showed widespread cerebral cortical diffusion abnormality with no infarction, bleeding or vascular abnormalities. Immediately after MRI, which was hours after the arrival to the emergency department, the patient suffered a generalized tonic-clonic seizure and was intubated because of respiratory distress. Arthrocentesis yielded purulent fluid that grew GAS. Blood cultures were negative as were imaging studies for thigh abscess or necrotizing fasciitis. The patient had a stormy ICU course complicated by acute respiratory distress syndrome (ARDS) and ventilator associated pneumonia (VAP). After 1 week of intensive treatment, he was slowly weaned off vasopressors and the ventilator. The patient's GAS isolate was M protein gene (emm) type 1 and T type 1.

He was discharged from the hospital to the acute rehabilitation facility on day 21, where he stayed 8 more days for rehabilitation. Twenty-nine days after admission to the ICU, he was discharged home. He maintained follow-up in the internal medicine clinic for several months where he initially complained of weakness, knee pain, diplopia and dry cough. His diplopia resolved within 4 months after discharge, followed by resolution of knee pain and cough. His symptoms resolved completely and he was able to return to work 8 months post discharge.

DISCUSSION

Toxic shock syndrome (TSS) is a toxin-related severe illness that occurs due to dysregulation of host inflammatory responses, causing hypotension and multi-organ failure.

Toxin-producing strains of *S. aureus* (including methicillin-resistant, MRSA) or Group A streptococcus (GAS) are the most common pathogens for TSS. Although uncommon, other bacteria, such as groups C and G β-hemolytic streptococci, *Clostridium* spp. and coagulase negative staphylococci may cause TSS as well. Furthermore, probable association with influenza infection has been described [1]. The annual incidence of invasive GAS infection has been estimated to be 1.4/100,000 population, of which TSS develop in 13% of patients [2]. Streptococcal TSS is primarily caused by skin and soft tissue infection (nearly 50%), followed by pneumonia. Approximately 15% of patients with TSS will have streptococcal bacteremia with no clear source. Streptococcal TSS is more common in patients who are younger than 50-years-old. Furthermore, chronic alcoholism, uncontrolled diabetes mellitus, varicella infection, and recent plastic surgery are recognized risk factors. Compared to staphylococcal TSS, most patients with streptococcal TSS have invasive syndromes such as necrotizing fasciitis, myonecrosis, or bacteremia. GAS causes TSS by producing superantigens, which are extracellular toxins that bypass antigen presentating cells, resulting in antigen-independent release of proinflammatory mediators and massive activation of T cells without major histocompatibility complex (MHC) class II restriction. Extensive inflammatory response and shock quickly ensue with widespread tissue damage and multi-organ dysfunction. Virulent factors responsible for invasive streptococcal disease and TSS include antiphagocytic proteins (called M proteins), cytotoxic toxins (A, B, C), and certain enzymes such as streptokinase and hyaluronidase. Among these factors, the M proteins (M1 and M3) and pyrogenic exotoxin A (80% of streptococcal TSS) are more likely to cause invasive GAS infection and TSS. The diagnosis of streptococcal TSS is made by fulfilling the diagnostic criteria (**Table**) [3]

Table. Diagnostic criteria of streptococcal TSS

A. Isolation of group A Streptococcus
1. From a sterile site
2. From a non-sterile site

B. Clinical signs of severity
1. Hypotension
2. ≥ 2 of the followings:
   a. Renal impairment
   b. Coagulopathy
   c. Liver abnormalities
   d. Acute respiratory distress syndrome
   e. Extensive tissue necrosis, ie. necrotizing fasciitis
   f. Erythematous rash

Definite Case = A1 + B (1+2)
Probable Case = A2 + B (1+2)

Source: Stevens DL. Invasive group A streptococcal infections: the past, present and future. *Pediatr Infect Dis J*. 1994; 13:561-6.

Patients with invasive streptococcal disease and TSS are typically very ill and, therefore, treatment should include empiric broad-spectrum antibiotics to cover potential pathogens (including coverage for both GAS and *S. aureus*) until GAS is confirmed. Other infections may produce signs and symptoms that can be confused with TSS and should be considered depending on the clinical context. These include leptospirosis, Rocky Mountain spotted fever and gram-negative sepsis. Prompt recognition and control of the infection source is of paramount importance (e.g. surgical debridement of necrotizing fasciitis). De-escalation to penicillin G (3 to 4 million units i.v. every 4 h) plus clindamycin (600 to 900 mg i.v. every 6 to 8 h) for 10 to 14 days is recommended [4]. Clindamycin, a protein synthesis inhibitor, may provide additional benefit by suppressing the production of M proteins and superantigens. Further, clindamycin has been shown (in animal models of streptococcal myositis) to be more effective than penicillin due to the "Eagle effect" of reduced expression of penicillin binding proteins by GAS during the stationary growth phase [5]. The use of intravenous immunoglobulin (IVIG) has been described in small series, and a survival benefit with IVIG therapy was reported in a Canadian observational study [6]. A multicenter, randomized, double-blind, placebo-controlled trial demonstrated significant decrease in sepsis-related organ dysfunction and a trend toward improved survival with IVIG (mortality at 28 days was 3.6-fold higher in the placebo group), which was not statistically significant [7].

Ischemic optic neuropathy (ION), also known as stroke of the optic nerve, is a devastating condition that results from transient ischemia of the optic nerve. ION can affect one eye or both eyes simultaneously. Two different forms of ION exist: arteritic form (seen mostly in elderly patients with hypoperfusion of the optic nerve due to large vessel vasculitis, eg. temporal arteritis); and non-arteritic ION (NAION) that can affect patients of any age and has been associated with transient hypotension presumably due to hypoperfusion of the paraoptic branches of the posterior ciliary artery. The incidence of NAION is 2.3–10.2 per 100 000 population in the United States [8]. Approximately 10% of non-arteritic ION occurs in individuals under the age of 45. The presence of atherosclerosis (e.g. due to diabetes mellitus), hypercoagulable state (e.g. anti-phospholipid antibody syndrome), or migraine increases the risk of NAION. Other risk factors include the traditional atherosclerosis risk factors such as smoking and hyperlipidemia. NAION presents with a rapidly progressive painless loss of vision (hours to days), usually described as dimness or blurring of the visual field.

Hypotension from any cause can result in NAION; this includes septic shock (as seen in our patient), hemorrhagic shock, or drug-induced hypotension (esp. beta blockers). In fact, several non-antihypertensive medications have been described to cause NAION, such as interferon-alpha, amiodarone, and phosphodiesterase-5 inhibitors [9]. NAION remains stable in the majority of patients, although some

recovery of vision can be expected in up to 42% of patients [10]. The development of NAION may signify the presence of diffuse vasculopathy, and may be associated with increased risk of strokes and cardiovascular events [11]. Treatment of NAION is largely supportive and consists of prompt recognition and correction of shock. The role of other therapies (e.g. aspirin or corticosteroids) remains to be elucidated.

CONCLUSION

Streptococcal pharyngitis is an exceedingly rare cause of TSS. In our patient, it was most likely the source of a transient bacteremia seeding the knee joint, a process that probably was occurring as he was evaluated for pharyngitis. The rapidity of the development of shock is attributed to streptococcal exotoxins acting as superantigens, directly unleashing host inflammatory responses. GAS type M1 (our patient's type) is commonly associated with severe shock in TSS. The profound hypotension was the likely cause of his ischemic optic neuropathy, which fortunately was reversible as he regained full vision. Early recognition and aggressive management that keep pace with the evolution of TSS are crucial to improve clinical outcome.

References

1. MacDonald KL, Osterholm MT, Hedberg CW, et al. Toxic shock syndrome. A newly recognized complication of influenza and influenzalike illness. JAMA. 1987;257:1053–8.
2. Eriksson BK, Andersson J, Holm SE. Epidemiological and clinical aspects of invasive group A streptococcal infections and the streptococcal toxic shock syndrome. *Clin Infect Dis*. Dec 1998;27(6):1428-36.
3. Stevens DL. Invasive group A streptococcal infections: the past, present and future. Pediatr Infect Dis J. 1994; 13:561-6.
4. Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Gold- stein EJ, Gorbach SL, Hirschmann JV, Kaplan EL, Montoya JG, Wade JC, Infectious Diseases Society of America. 2005. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin. Infect. Dis. 41:1373–1406.
5. Stevens DL, Gibbons AE, Bergstrom R, Winn V. 1988. The Eagle effect revisited: efficacy of clindamycin, erythromycin, and penicillin in the treatment of streptococcal myositis. J. Infect. Dis. 158:23–28.
6. Kaul R, McGeer A, Norrby-Teglund A, Kotb M, Schwartz B, O'Rourke K, Talbot J, Low DE. 1999. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome—a comparative observational study. The Canadian Streptococcal Study Group. Clin. Infect. Dis. 28: 800 – 807.
7. Darenberg J, Ihendyane N, Sjolin J, Aufwerber E, Haidl S, Follin P, Andersson J, Norrby-Teglund A. 2003. Intravenous immunoglobulin G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. Clin. Infect. Dis. 37:333–340.
8. Hattenhauer MG, Leavitt JA, Hodge DO, Grill R, Gray DT. Incidence of nonarteritic anterior ischemic optic neuropathy. Am J Ophthalmol.1997;123: 103–107.
9. Pomeranz HD, Smith KH, Hart Jr WM, Egan RA. Sildenafil-associated nonarteritic anterior ischemic optic neuropathy. Ophthalmology. 2002; 109: 584–587.
10. Ischemic Optic Neuropathy Decompression Trial Research Group. Optic nerve decompression surgery for nonarteritic anterior ischemic optic neuropathy (NAION) is not effective and may be harmful. JAMA.1995; 273: 625–632.
11. Guyer DR, Miller NR, Auer CL, Fine SL. The risk of cerebrovascular and cardiovascular disease in patients with anterior ischemic optic neuropathy. Arch Ophthalmol. 1985;103: 1136–1142.

Authors

Salaheldin M. Elhamamsy MD, Department of Medicine, Memorial Hospital of Rhode Island, Alpert Medical School of Brown University.

Mazen O. Al-Qadi, MD, Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, Memorial Hospital of Rhode Island, Alpert Medical School of Brown University.

Taro Minami, MD, Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, Memorial Hospital of Rhode Island, Alpert Medical School of Brown University.

Marguerite Neill, MD, Department of Medicine, Division of Infectious Diseases, Memorial Hospital of Rhode Island, Alpert Medical School of Brown University.

Correspondence

Mazen O. Al-Qadi, MD
401-834-0709
mazen_al-qadi@brown.edu