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Case Report

Toxic shock syndrome due to group A streptococcal pharyngitis and bacteremia in adults

Zeljko Vucicevic[1], Ines Jajic-Bencic[2], Bozo Kruslin[3], Vesna Degoricija[1]

[1]Department of Emergency Medicine, University Department of Medicine; [2]Department of Microbiology; and [3]Department of Pathology, Sestre Milosrdnice University Hospital, Zagreb, Croatia

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Bacteremia and/or toxic shock syndrome are rare complications of streptococcal pharyngitis in adults. This report describes a previously healthy young man with streptococcal toxic shock syndrome who presented with fatigue, high fever, and suspected extensive streptococcal tonsillopharyngitis. Treatment consisted of high-dose antibiotics followed by therapy for consumptive coagulopathy, acute renal failure, and toxic shock syndrome. An attempt at hemodialysis and hemodiafiltration was ineffective, and the patient died within 24 h of admission. The autopsy findings were compatible with the clinical diagnosis. The invasive group A streptococci isolated from the pharyngeal swab and blood cultures were identified as M1 and T1 types with pyrogenic exotoxin genes A and B. This was a definitive case of streptococcal toxic shock syndrome complicated with multiorgan failure and fatal outcome. The benefits of intravenous immunoglobulins, surgical intervention, or clindamycin for improving survival remain to be evaluated.

Key words: Pharyngitis; Shock, septic; *Streptococcus pyogenes*

Introduction

Group A streptococcus (GAS, *Streptococcus pyogenes*) is an aerobic Gram-positive coccus that causes pharyngitis and a spectrum of skin and soft tissue infections, such as impetigo, erysipelas, and localized cellulitis [1]. GAS toxic shock syndrome (GAS TSS) is defined as any GAS infection associated with the onset of shock and organ failure.

In the mid-1980s, invasive infections associated with GAS TSS were reported with increasing frequency from Europe and North America [2,3]. From July 1, 1995 through December 31, 1999, 2002 patients with invasive GAS disease were identified in 5 United States surveillance areas [4]. The average annual incidence of invasive GAS disease for these years was 3.5/100,000 population. Bacteremia associated with GAS pharyngitis is uncommon and, even with scarlet fever, bacteremia-associated GAS occurs in only 0.3% of febrile patients [5].

Patients with symptomatic pharyngitis rarely develop GAS TSS as a complication [6]. This report is of a previously healthy young man with streptococcal pharyngitis followed by GAS TSS and fatal outcome.

Case Report

A previously healthy 19-year-old man was referred to the Sestre Milosrdnice University Hospital, Zagreb, Croatia, at 13:00 on January 10, 2002 with fatigue and high fever of up to 40.3°C. The fever and malaise started on the previous evening, only a few hours after he took part in a soccer game. His past medical history did not show any relevant illnesses, with the exception of mild allergic asthma, which was maintained by occasional inhalations of salbutamol.

On arrival, the patient was well orientated, febrile (38.3°C), prostrated, normotensive, and eupneic, with a heart rate of 80 beats per min. Intense erythema and swelling of the pharynx, and a purulent exudate over the posterior pharyngeal wall and tonsillar pillars was noted,

Corresponding author: Dr. Zeljko Vucicevic, Department of Emergency Medicine, University Department of Medicine, Sestre Milosrdnice University Hospital, Vinogradska Cesta 29, Zagreb 10000, Croatia.
E-mail: zeljko.vucicevic@zg.t-com.hr

but the patient did not have a sore throat. No other abnormalities were present at physical examination.

Electrocardiography and chest radiographic findings were within normal limits. The values of urgent laboratory tests were as follows: erythrocyte sedimentation rate, 5 mm/h; white blood cell count, 19.5 × 10^9/L with a strong 'shift to the left'; platelet count, 191 × 10^9/L; creatine kinase (CK), 1128 U/L; aspartate transaminase (AST), 123 U/L; alanine transaminase (ALT), 59 U/L; lactic acid dehydrogenase (LDH), 936 U/L; bilirubin, 44.4 µmol/L; blood glucose, 9.4 mmol/L; activated partial thromboplastin time (APTT), 52 sec; prothrombin time (PT), 37% or international normalized ratio (INR), 2.0; and fibrinogen, <0.1 g/L. The acid-base balance of capillary blood and serum creatinine level were normal.

On suspicion of extensive acute streptococcal tonsillopharyngitis and consumptive coagulopathy, and concern for further deterioration, the patient was admitted to the intensive care unit at 14:00.

The patient was given clindamycin 900 mg intravenously (IV) every 6 h, crystacillin bolus 600,000 IU IV, and crystacillin infusion at a rate of 400,000 IU/h. Apart from volume replacement and Venturi mask oxygenation, fresh frozen plasma and low-molecular weight heparin were started to control disseminated intravascular coagulation. The patient became hypotensive (90/60 mm Hg) 3 h after admission and was given dopamine 5 µg/kg/min, but a satisfactory systemic pressure was not reached. The patient was oliguric with a consecutive rise in creatinine level. At 22:00 severe deterioration occurred, with the following laboratory results: leukocytes, 3.3 × 10^9/L; platelet count, 29.0 × 10^9/L; APTT, 214 sec; PT, 7% or INR, 5.2; AST, 238 U/L; ALT, 63 U/L; LDH, 3230 U/L; bilirubin, 97.6 µmol/L, and the previously normal acid-base balance became severe metabolic acidosis.

The findings were indicative of refractory toxic shock syndrome. An attempt at hemodialysis and hemodiafiltration was ineffective and the patient died at 13:00 on the following day, exactly 24 h after admission.

The autopsy revealed multiple small hemorrhages affecting the skin and mucous membranes. There was bilateral pleural effusion, mainly on the right side (1000 mL). The lungs were heavy, firm, and red. The right coronary artery was hypoplastic.

Microscopic examination showed congestion of the lung with intra-alveolar and interstitial edema, fibrin deposition, and extensive hemorrhages (Fig. 1). Inflammatory infiltrates composed of neutrophils and lymphocytes were present in the alveolar septa and some adjacent alveoli. The septa were lined with hyaline membranes. Numerous fibrin thrombi were observed in the glomerular capillaries in both kidneys, suggesting disseminated intravascular coagulation (Fig. 2).

Pharyngeal swab and blood cultures were taken before the antibiotic regimen was instituted, and the results were obtained postmortem. Blood cultures were analyzed using the BacT/Alert system and, after 24 h, yielded Lancefield group A streptococci as identified by β-hemolysis and latex agglutination (Slidex Strepto-Kit; BioMérieux, Marcy-l'Etoile, France). Disk diffusion test showed susceptibility to penicillin G, azithromycin, and clindamycin. Bacteriologic analysis of the pharyngeal swab also demonstrated *S. pyogenes*. Further examinations of the 2 specimens

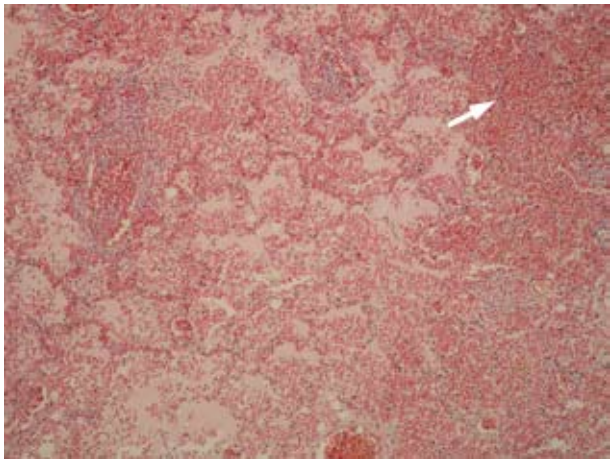

Fig. 1. Congestion of the lung with intra-alveolar and interstitial edema, fibrin deposition, and extensive hemorrhages (arrow) [hematoxylin and eosin stain; × 100].

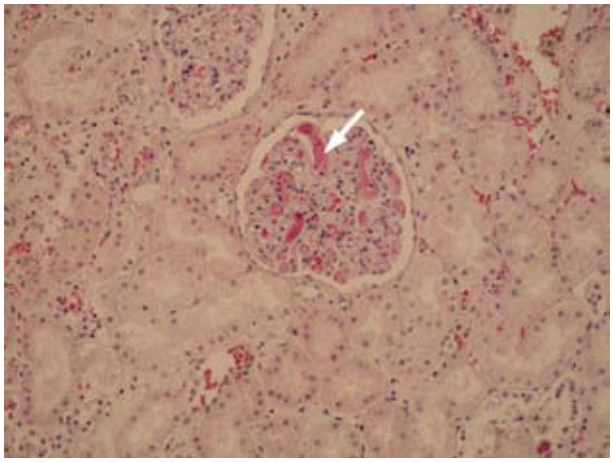

Fig. 2. Numerous fibrin thrombi (arrow) in the glomerular capillaries suggesting disseminated intravascular coagulation (hematoxylin and eosin stain; × 200).

at the Public Health Laboratory Service, Streptococcus and Diphtheria Reference Unit in London, UK, identified the GAS as M1 and T1 type possessing 2 pyrogenic exotoxin genes, A and B.

Discussion

The M protein numbers more than 80 different serotypes, and is an important virulence determinant of GAS. The M protein is a filamentous protein anchored to the cell membrane with antiphagocytic properties. GAS strains lacking in M protein are less virulent. The M types 1, 3, 12, and 28 occur most commonly in patients with shock and multiorgan failure [7]. The pyrogenic exotoxin genes A and B, produce the streptococcal pyrogenic exotoxins A and B, respectively (SPEA and SPEB). SPEA and SPEB may lower the threshold for exogenous endotoxin and act as superantigens. SPEA is characteristically associated with shock, acute respiratory distress syndrome, renal failure, and tissue destruction [6].

The acquisition of type-specific anti-M-protein antibody provides some protection, but the sequence of M1 protein varies sufficiently that antibody against one strain of M1 is not protective against another [8]. The epidemiological factors, clinical syndrome, and outcome of infection are determined by the interaction between these microbial virulence factors and an immune or non-immune host.

According to the 1993 consensus definition of the Working Group on Severe Streptococcal Infections, this patient's illness meets criteria IA, IIA and IIB, and may be defined as a definitive case of streptococcal TSS [9].

Bacteremia and TSS are rare following GAS pharyngitis [6,8]. A study by Barnham, which was designed to detect bacteremia in patients with a sore throat, showed that 93 of the 343 patients tested yielded β-hemolytic streptococci from the respiratory tract, but no patients had streptococcal bacteremia [10]. These results suggest that clinically unsuspected streptococcal bacteremia is uncommon in such patients.

The mainstay of therapy for GAS TSS is penicillin G. However, penicillin may become less effective when high concentrations of GAS are present or when they are in transition from the logarithmic to the stationary phase of growth. In such cases, treatment with clindamycin offers several advantages [11-13]:

- the efficacy of clindamycin is not affected by inoculum size or stage of growth;
- clindamycin suppresses the synthesis of bacterial toxins;
- clindamycin facilitates phagocytosis of *S. pyogenes* by inhibiting synthesis of the antiphagocytic M-protein;
- clindamycin suppresses the synthesis of penicillin-binding proteins, which, in addition to being targets for penicillin, are involved in cell wall synthesis and degradation; and
- clindamycin produces a longer postantibiotic effect than β-lactam antibiotics such as penicillin.

A retrospective analysis demonstrates that in patients with GAS TSS, the use of clindamycin is associated with better outcomes than β-lactam antibiotics.

Definitive studies that would help to establish the most effective antibiotic regimen for GAS TSS are not available. A strong suspicion of GAS TSS in this patient called for an empirical antibiotic therapy consisting of clindamycin and penicillin G. There are no known additive, synergistic, or antagonistic effects of penicillin when it is added to clindamycin in vitro. Penicillin is also useful in rare cases of GAS resistance to clindamycin [14].

A study by Valiquette et al showed that 172 of 190 infectious disease specialists (90.5%) would recommend intravenous administration of immunoglobulins (IVIG) for the management of streptococcal TSS [15]. However, Mehta et al reported an overall mortality rate of 40% for patients with invasive group A streptococcal infections who were admitted to the intensive care unit [16]. In those patients, coagulopathy and liver failure were independently associated with mortality. No association between the use of IVIG, surgical intervention, or clindamycin, and survival was observed.

Well known for its fulminant severe course and high mortality rate, streptococcal TSS calls for urgent diagnostic and therapeutic approaches to improve the rate of survival.

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