

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

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Bacteremia and/or toxic shock syndrome is a rare complication of streptococcal pharyngitis in adults. We describe a case of streptococcal toxic shock syndrome in a previously healthy young man who presented with fatigue, high fever, and suspected extensive streptococcal tonsillo-pharyngitis. Therapy consisted of high doses of antibiotics followed by treatment of consumptive coagulopathy, acute renal failure, and toxic shock syndrome. An attempt at hemodialysis and hemodiafiltration was ineffective, and the patient died 24 h after 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 type with pyrogenic exotoxin genes A and B. This was thus a definite case of streptococcal toxic shock syndrome complicated with multiorgan failure and lethal outcome. The benefit of intravenous immunoglobulins, surgical intervention, or clindamycin in survival improvement remains to be evaluated.

Key words: Male; Pharyngitis; Shock, septic; Streptococcal infections; *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 (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]. Since then, the prevalence has been approximately 3.5 cases per 10,000 people, with up to one-third of the cases developing GAS TSS [4]. Bacteremia in association with GAS pharyngitis is uncommon, and even during scarlet fever it occurs in only 0.3% of febrile patients [5].

Patients with symptomatic pharyngitis rarely develop GAS TSS as a complication [6]. We present a case of a previously healthy young man with streptococcal pharyngitis followed by GAS TSS with lethal outcome.

Case Report

A previously healthy 19-year-old man was referred to our hospital at 1.00 p.m., because of fatigue and a high fever of up to 40.3°C. The fever and malaise had occurred on the previous evening, a couple of hours after he took part in a soccer game. The past medical history did not show any relevant illnesses with the exception of mild allergic asthma which was maintained by occasional inhalation of salbutamol.

Upon arrival, the patient was well orientated, febrile (38.3°C), prostrated, normotensive and eupnoic with a heart rate of 80/min. Intense erythema and swelling of the pharynx and a purulent exudate over the posterior pharyngeal wall and tonsillar pillars was noted, but the patient offered no complaints of a sore throat. No other abnormalities were present at physical examination.

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Electrocardiogram and chest X-ray findings were within normal ranges. The values of urgent laboratory tests were as follows: erythrocyte sedimentation rate 5 mm/h, white blood cell count $19.5 \times 10^9/L$ with a strong “shift to the left”, platelet count $191 \times 10^9/L$, creatine kinase 1128 U/L, aspartate aminotransferase 123 U/L, alanine aminotransferase 59 U/L, lactate dehydrogenase 936 U/L, bilirubin 44.4 $\mu\text{mol/L}$, glucose in blood 9.4 mmol/L, activated partial thromboplastin time 52 min, prothrombin time 37% or international normalized ratio 2.0, and fibrinogen $<0.1 \text{ g/L}$. The acid-base balance of capillary blood and serum creatinine level were normal.

For suspicion of extensive acute streptococcal tonsillo-pharyngitis, and consumptive coagulopathy and for fear of further deterioration, the patient was admitted to the intensive care unit at 2.00 p.m.

Therapy consisted of intravenous clindamycin 900 mg every 6 h, intravenous crystacillin bolus (600,000 IU) and crystacillin infusion at the rate of 400,000 IU/h. Apart from volume replacement and Venturi mask oxygenation, fresh frozen plasma and low-molecular-weight heparin were started in order to control disseminated intravascular coagulation. Hypotension (90/60 mm Hg) occurred three hours later and dopamine (5 $\mu\text{g/kg/min}$) was given, but a satisfactory systemic pressure was not reached. The patient was oliguric with a consecutive increase in creatinine level. At about 10.00 p.m., severe worsening of laboratory values was observed as follows: leukocytes and platelet count $3.3 \times 10^9/L$ and $29.0 \times 10^9/L$, respectively, activated partial thromboplastin time 214 min, prothrombin time 7% or international normalized ratio 5.2, aspartate aminotransferase 238 U/L, alanine aminotransferase 63 U/L, lactate dehydrogenase 3230 U/L, bilirubin 97.6 $\mu\text{mol/L}$, accompanied by severe metabolic acidosis.

The findings were indicative of refractory TSS. An attempt at hemodialysis and hemodiafiltration was ineffective and the patient died at 1.00 p.m. the following day, exactly 24 h after admission.

Autopsy revealed multiple small hemorrhages affecting 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 oedema, fibrin deposition and extensive hemorrhages (Fig. 1). Inflammatory infiltrates composed of neutrophils and lymphocytes

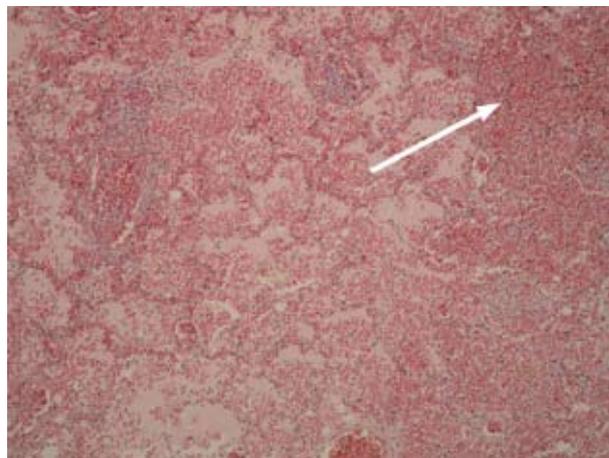


Fig. 1. Photomicrograph showing congestion of the lung with intra-alveolar and interstitial edema, fibrin deposition and extensive hemorrhages (hematoxylin and eosin stain, $\times 100$).

were present in the alveolar septa and some adjacent alveoli. The septa were lined with hyaline membranes. Numerous fibrin thrombi were observed in 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 post mortem. Blood cultures were analysed in the BacT/Alert system and after 24 h yielded Lancefield group A streptococci as identified by beta-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 pharyngeal swab also demonstrated *S. pyogenes*. Further examination of the two specimens at the Public

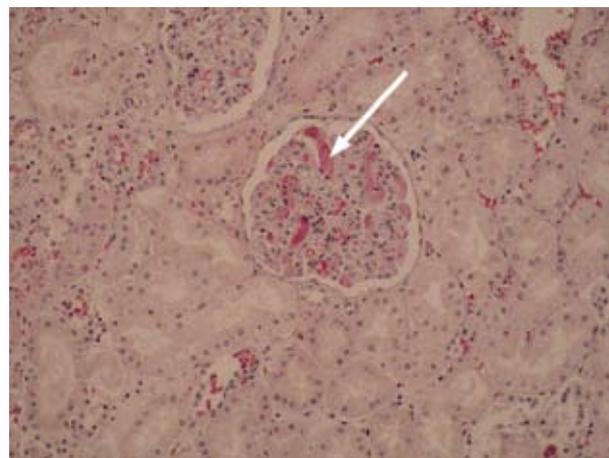


Fig. 2. Numerous fibrin thrombi can be seen in glomerular capillaries, suggesting disseminated intravascular coagulation (hematoxylin and eosin stain, $\times 200$).

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

Discussion

The M protein has over 80 different serotypes, and is an important virulence determinant of GAS. It is a filamentous protein anchored to the cell membrane with antiphagocytic properties. The strains lacking in M protein are less virulent. 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. Streptococcal pyrogenic exotoxin A and B may lower the threshold for exogenous endotoxin and act as superantigens. Streptococcal pyrogenic exotoxin A is characteristically associated with shock, adult respiratory distress syndrome, renal failure, and tissue destruction [6].

The acquisition of type-specific anti-M protein antibody provides certain 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, the illness of our patient meets the criteria IA, IIA and IIB, and may be defined as a definite 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 patients of the 343 tested yielded beta-hemolytic streptococci from the respiratory tract, but none had streptococcal bacteremia. These results suggest that clinically unsuspected streptococcal bacteremia is uncommon in such patients [10].

The mainstay of GAS TSS therapy is penicillin G. However, penicillin may become less effective when high concentrations of GAS are present or when the infection is in the 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
- clindamycin produces a longer postantibiotic effect than beta-lactams such as penicillin
- a retrospective analysis demonstrates that, in GASS TSS patients, the use of clindamycin is associated with better outcomes than beta-lactam antibiotics.

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

A study by Valiquette et al showed that 90.5% (i.e., 172 out of 190) of infectious disease specialists would recommend intravenous administration of immunoglobulins in the management of streptococcal TSS [15]. However, Mehta et al reported an overall mortality rate of 40% in 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 intravenous immunoglobulins, surgical intervention, or clindamycin and survival was observed.

Because of its fulminant, severe course and high mortality rate, streptococcal TSS calls for an urgent diagnostic and therapeutic approach in order to maximize the rate of survival.

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