An exceptional case of Streptococcal Toxic Shock Syndrome

BM van der Oord¹, C Hoï², B Manten¹

1 Department of Intensive Care Medicine, Meander Medical Centre, Amersfoort, The Netherlands
2 Department of Microbiology, Meander Medical Centre, Amersfoort, The Netherlands

Abstract · Streptococcal Toxic Shock Syndrome (TSS) is caused by an infection with Group A Streptococcus (GAS). Streptococcal pyrogenic exotoxins type A (SPEA) and/or type B (SPEB) are found in the majority of cases of severe GAS infections and play an important role in virulence. These exotoxins can activate the immune system by bypassing the usual antigen-mediated immune response sequence, resulting in the release of large quantities of inflammatory cytokines. These cytokines cause capillary leak and tissue damage, leading to shock and Multi Organ Failure. Overall mortality is 30 to 80 percent, despite aggressive modern therapy [1,2,3,4]. Even though early symptoms can be vague and unspecific, as in our case, it is important to suspect and diagnose TSS at an early stage, because early treatment may have a beneficial effect on outcome.

Keywords · Streptococcal Toxic Shock Syndrome, TSS, immunoglobulin-therapy

Introduction
Group A Streptococcus is an aerobic gram positive coccus, also known as S.pyogenes, that can cause severe skin and soft tissue infections and lead to multiple organ failure. Group A Streptococcal TSS is defined as any Group A Streptococcus infection associated with the acute onset of shock and organ failure. Most common portals of entry (chronically colonized sites) are the skin, pharynx, rectum, vagina, or cervix – though strep TSS is also a rare complication of pharyngitis. In 45 percent of patients who develop severe GAS infection, a portal of entry cannot be identified.

The infection may start at a site of minor trauma or injury, after surgical procedures, or develop alongside a viral infection such as varicella or influenza. The most common presenting symptom of necrotizing fasciitis, in cases in which this complication develops in an invasive GAS infection is abrupt, severe pain on the affected site, with a lack of visible abnormalities on examination though sometimes a deep painful diffuse infiltrate may be palpated. Early systemic manifestations include an influenza-like syndrome, fever, myalgia and often confusion (55%) [1]. Clinical signs of soft tissue infection, such as localized swelling and exanthema, occur in 80 percent of patients. The exanthema will be diffuse and scarlatina-like in only 10 percent of cases.

Laboratory findings include a high percentage of immature neutrophils, elevated serum creatinine and serum creatine kinase, myoglobinuria and haemoglobinuria (due to toxin-induced haemolysis) and, together with hypotension, may lead to acute renal failure. Shock, Diffuse Intravascular Coagulopathy (DIC) and Acute Respiratory Distress Syndrome (ARDS) can develop. Hypoalbuminaemia and disproportional hypocalcaemia often occur. In approximately 60 percent of cases positive blood cultures will be present. In this case report, we will present a patient with fatal strep TSS from an unexpected, and not yet described origin.

Case
A 56-year-old man with a medical history of liver cirrhosis (Child-Pugh B) due to alcohol abuse, and hypertension, was sent to the emergency room because of rapidly developing dyspnoea and swelling of the left cheek. He had been healthy before this hospital visit with no history of recent complaints. No dental problems were mentioned and the patient had his own teeth; dentist check-up status was uncertain. His first symptoms had started about 24 hours before and consisted of spontaneous and sudden severe pain, worsening with movement of the jaw, without initial swelling. Before presenting to the emergency room, rapid swelling of the left cheek which spread to the side and below the mandible developed, accompanied by local but spreading exanthema. All this did not react to antibiotics prescribed by the patient’s GP. According to NGH standards for soft tissue infections, Fiucloxacinil was started: 4dd 500mg orally. As the swelling progressed further to the neck swallowing became difficult and dyspnoea began.

In the emergency room physical examination of the patient showed a very dyspnoeic obese man (100kg/178cm) with threatened upper airway due to severe swelling with dark red erythema. The swelling was very painful at bimanual palpation. No signs of pharyngitis were present. Blood pressure was low at 110/45, pulse rate 118/min r.a. and central body temperature (37.3 C) was normal. Heart and pulmonary auscultation revealed no abnormalities, only gynecomastia was obvious. The abdomen was obese with hepatosplenomegaly, spider naevi and some ascites. There was erythema palmar of both hands. Blood samples were drawn and the patient was intubated and transported to the ICU.

Laboratory values: Hb 7.3 mmol/l, Leucocytes 2.5 x10 9/l, Lymphocytes 10.0 %, Thrombocytes 28. CRP 44 mg/l, Sodium 126 mmol/l, Potassium 3.1 mmol/l, Calcium 1.21 mmol/l, Urea 15.2 mmol/l, Creatinine 184 umol/l, Albumine 17 g/l, Glucose 8.9
mmol/l, Lactate 4.5, PT-INR 2.1, APTT 53, CRP, though elevated, did fail to show the severity of the disease, whereas lymphopenia was profound. No prior data were available for this patient.

At the ICU the patient’s condition deteriorated fast with development of severe hypotension and ARDS, no reaction to volume resuscitation. Inotropics were started, as well as hydrocortisone and antibiotics. Based on the possible etiological microbial agents in this rapidly deteriorating swelling of the neck in this patient, such as oral anaerobes, S.aureus, group A.streptococcus and H.influenzae, a choice was made for augmentin and ciprofloxacin. A puncture of the local swelling revealed no bacteria, maybe due to the GP’s earlier treatment with antibiotics.

Blood cultures also failed to show any bacterial growth, again probably because of the early start of antibiotics. Because the exact diagnosis was not yet known, after some stabilisation, a CT-scan of the head and neck (figures I and II) was made that showed impressive parapharyngeal infiltration on the left side, but no abscess, subcutaneous emphysema or thrombophlebitis were seen.

There were no evident signs of fasciitis necroticans, but an obstruction of the submandibular gland was suspected. The ear-nose-throat specialist was asked to make the case and diagnosed this obstruction of the left submandibular gland as an impressive salivary stone. The infiltrated region was incised and drained of purulent fluid for bacterial culture that revealed only S.pyogenes. This S.pyogenes with pyrogen toxin production, confirmed by the RIVM, showed a polysaccharide type B of the outer wall. At drainage there were no signs of fasciitis necroticans. Antibiotic strategy was changed to Benzylpenicillin 12 milj U/24 hours continuously and Clindamycin 3dd 600mg intravenously. Because of total renal failure Continuous Veno-Venous Haemofiltration (CVVH) was started and antibiotics were given in adjusted dosages (Benzylpenicillin 9 milj U/24 hours = 75% of normal dosage and Clindamycin unadjusted). While inotropic therapy had to be severely increased due to a deteriorating situation, as a last option to treatment, intravenous immunoglobulin was given (Nanogan 2 gram/kg) [5]. Therapy changes did not result in any improvement of the situation after almost 72 hours of treatment, with progressive ischaemia of limbs due to circulation failure and the necessary high doses of inotropics. It was then decided to cease treatment. Autopsy showed an acute necrotizing infection of the larynx, soft tissue and fasciae of the neck, most impressive around the area of the submandibular gland. The liver, heart and spleen showed haemochromatosis, and the liver and heart had signs of moderate damage due to alcohol (cirrhosis, cardiomyopathy). All organs showed signs of severe sepsis.

Discussion

In retrospect, because of the patient’s severe condition (disorientation, difficult speech) when presented to our hospital, there were only a few anamnestic clues as to where this sudden and rapidly progressive infection originated from. It took some time to suspect and prove the diagnosis of strep TSS from this peculiar site, until gram stain and culture showed the presence of S.pyogenes. We know, however, that S. pyogenes is an important cause of respiratory infections (nasopharyngitis, tonsillitis and scarlatina). The differential diagnosis should also consider infection by oral anaerobes (Plaut Vincent and Ludwig’s angina), unilateral Strep erysipelas of the cheek, Lemiére’s syndrome, H.influenza (para-)diffuse pharyngitis/epiglottitis/cellulites, S.aureus and/or streptococcal infection of a salivary stone. In our case there were only few symp-

**Figure 1.** Impressive parapharyngeal infiltration on the left side, but no abscess or signs of fasciitis necroticans.

**Figure 2.** Obstruction of the left submandibular gland by an impressive salivary stone.
toms characteristic for primary submandibular gland infection.

All general principles in the management of septic shock were started as soon as possible. These included the following:

- early recognition
- early and effective antibiotic therapy
- source control (surgical drainage is the single most important measure in cases of an abscess or obstructed organ/gland)
- early haemodynamic resuscitation and continued support
- corticosteroids (refractory vaspressor-dependent shock)
- tight plasma glucose-control
- proper ventilator management with low tidal volume in patients with ARDS
- CVVH in renal failure
- Vitamin substitution for alcohol addiction (thiamine).

Although the antibiotic therapy that had been started in an early phase was sufficient, it could have been even more directed towards this specific type of infection. This was adjusted as soon as the correct diagnosis confirmed by bacterial culture was known. Benzylpenicillin was started, which is known to be very effective in streptococcal infections. Clindamycin was added because of its potent suppression of bacterial toxin synthesis and facilitation of phagocytosis of S. pyogenes by inhibiting M-protein synthesis. As further deterioration of the patient was noticed, immunoglobulin therapy was started because of its possible neutralizing effects on toxins already produced and the positive effect on opossum-phagocytosis. Where antibiotics stop bacterial growth and thus the production of further toxins, the toxins already produced can still harm the patient. When toxin-concentration drops, the stimulation of interleukin production and proliferation of T-lymphocytes is down-regulated as well [6-9]. It must be stated that there are only limited clinical data for the additional treatment with iv immunoglobulins [10,11].

We started giving immunoglobulins at 2 nanogram/kg in the first 24 hours of admission and continued for 48 hours.

One further point that should be noted concerns the risk factors for strep TSS, including diabetes and alcoholism. Though persons of all ages may be affected by this condition – most of whom are not immunosuppressed [2,12-17] – people with cardiovascular disease, collagen vascular disease (with or without steroid use), trauma and alcoholism (as in our patient with Child-Pugh B liver cirrhosis) show higher rates of infection [17]. A case control study showed the highest odds ratios (OR) for the following independent risk factors: cirrhosis (OR 9.7), breast cancer (OR 4.0), stroke (OR 3.5), diabetes mellitus (OR 3.0).

This type of infection is equally prevalent in men and women, prevalence rates are 1.5 cases/100,000 people/year. Though data support the use of chemoprophylaxis in patients’ close contacts, it is unclear whether the goal is to prevent the disease in those recently colonized or to decrease transmission of a strain known to cause severe infection [18].

Many cases of streptococcal pharyngitis, erysipelas, scarlet fever, acute rheumatic fever and post streptococcal glomerulonephritis have been published. A rapidly fatal infection due to obstruction of a submandibular gland has (as far as we know) not been described in literature before. Even though this type of infection is rather rare, we have to take it into consideration each time a very serious and rapidly progressive case like this is treated in our hospital.

References