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Case Report

Severe group A streptococcal toxic shock syndrome presenting as primary peritonitis: a case report and brief review of the literature

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ABSTRACT

Streptococcal toxic shock syndrome (STSS) can be defined as a septic shock syndrome resulting from infection with toxin-producing group A streptococci (GAS). STSS can sporadically present as primary peritonitis in previously healthy persons. Signs of STSS are non-specific and patients generally present with flu-like symptoms and can develop a life-threatening toxic shock syndrome in just a few hours. Diagnosis is mainly by a combination of physical examination, laboratory/culture results, and exclusion of surgical causes by means of imaging modalities and/or surgical exploration. GAS remain penicillin-sensitive and most are clindamycin-sensitive. Prompt supportive treatment, possibly together with high-dose intravenous immunoglobulins, is crucial.

1. Introduction

Lancefield group A β-hemolytic Streptococcus (GAS) also known as *Streptococcus pyogenes*, is known to cause several diseases of varying clinical severity. Well-described and frequently observed suppurative infections caused by *S. pyogenes* are pharyngitis and skin infections like erysipelas and impetigo, with necrotizing fasciitis being the most severe presentation. Other dramatic manifestations are puerperal sepsis and the rare streptococcal toxic shock syndrome (STSS), which resembles the staphylococcal toxic shock syndrome. In addition, non-suppurative infections, such as rheumatic fever and acute glomerulonephritis, have been associated with GAS.

Virulence is determined by the presence or absence of encapsulation, adhesion proteins, toxin production, and host factors.[1,2]

Several epidemiological studies have indicated that GAS infections are increasing in incidence and are becoming more severe in presentation.[3,4]

STSS can sporadically present in previously healthy people as primary peritonitis, with severe septic shock and multiple organ failure emerging in just a few hours.[5] A few such cases have been described thus far, occurring especially in women of reproductive age; an association with the female genital tract has therefore been speculated.

Here we present a case of STSS and briefly review potential characteristics, difficulties in diagnosis, and treatment options for this potentially fatal syndrome.

2. Case report

A 39-year-old woman was referred to our tertiary care university hospital from a nearby hospital. The patient had presented there with 'flu-like' symptoms including headache, fever (up to 38.5 °C), and anorexia. Two days later she developed cold shivers, nausea with vomiting, and diarrhea (about 10 times a day without blood or mucus). Furthermore she complained of an abrupt onset severe muscle pain in the right medial thigh, radiating to the right lower abdomen, which prevented her from walking within hours of onset. There was no history of cough or dyspnea in the days before presentation. Her children had had remarkably red lips for about 2 weeks and had suffered for some days from sore throat.

Her last menstruation had been two weeks ago and she had normal regular menses. There was no history of abnormal vaginal discharge or dysuria, although she claimed that micturition was less than normal the day before presentation. Her medical history was unremarkable, except for an appendectomy in 1984, and her family history was unremarkable. She is a general physician and mother of four children. There was no recent travel history or

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Table 1
Laboratory results

Characteristic	On admission (nearby hospital)
Blood count	
Hemoglobin	5.7 mmol/l
Mean corpuscular volume (MCV)	74 fl
Leukocytes	2.8×10^9/l
Neutrophils	Normal
Rods in the white cell differentiation	38%
Lymphocytes	0.06×10^9/l
Thrombocytes	130×10^9/l
C-reactive protein (CRP)	296 mg/l
Urea	11.6 mmol/l
Creatinine	159 mmol/l (MDRD 31 ml/min)
Liver biochemistry	
Bilirubin	21.3 mmol/l
Aspartate aminotransferase (AST)	108 mmol/l
Alanine aminotransferase (ALT)	65 mmol/l
Blood gas analysis	
Ph	7.38
pCO_2	26 mmHg
HCO_3^-	15 mmol/l
Base excess (BE)	−10 mmol/l
Lactate	5.3 mmol/l
Urine	No abnormalities

MDRD, Modification of Diet in Renal Disease Study equation.

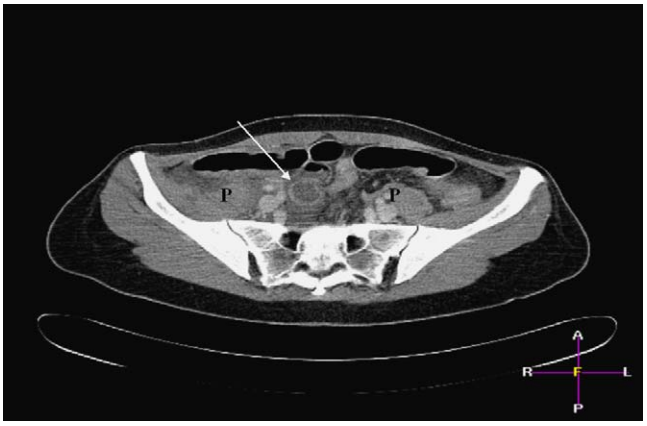

Figure 1. Thickened psoas muscle (P) and enlarged adnexal region with a prominent cyst (arrow) on the right. Compare with normal psoas muscle (P) on the left.

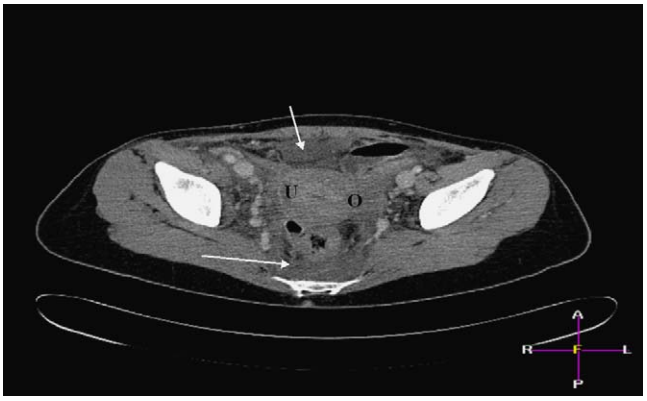

Figure 2. The left ovary (O) appears normal. Ascites in the pelvic cavity (arrows). U: uterus.

contact with animals or insect bites. There was no history of wounds, although she claimed that she had a long history of onychomycosis of the toes on both feet, for which she visited the chiropodist now and then. She did not take any medication.

On physical examination, she was seen to be ill looking and hypotensive, with resting blood pressure of 68/50 mmHg and pulse 104 bpm. Her temperature was 38.5 °C and arterial oxygen saturation 96% without supplemental oxygen. Skin turgor was diminished, and dry mucous membranes were observed. Lymph nodes were not palpable.. Heart sounds were normal and an examination of the lungs revealed some wheezes without crackles. The abdomen showed a diffuse exanthema, sparse peristalsis, normal tympania, and was soft on palpation without rebound pain. The liver and spleen were not palpable. There was a severe pain radiating from the right medial thigh to the right inguinal region and right lower quadrant of the abdomen. The extremities showed no erythema or edema. Raising the right leg was extremely painful, indicating a 'positive psoas' sign. An electrocardiogram showed a sinus tachycardia without further abnormalities. Laboratory results are summarized in Table 1.

Due to the suspicion of pelvic inflammatory disease (PID), a consultation with a gynecologist was arranged. A vaginal digital examination revealed no abnormalities and no discharge. On initial transvaginal ultrasound (TV US), the right ovary appeared enlarged. The left adnexal region showed no abnormalities. No fluid collections were seen in the Douglas cavity. A computed tomography (CT) scan of the thorax and abdomen 24 h after the initial TV US showed a thickened right psoas muscle surrounded by fatty infiltration and a large amount of free fluid in the peritoneal cavity (Figures 1 and 2). The patient was admitted to the intensive care unit (ICU) and received resuscitation fluids, inotropic support, and intravenous antibiotics (amoxicillin–clavulanic acid 1.2 g four times daily, clindamycin 600 mg three times daily, and gentamicin 240 mg once daily). The patient was subsequently transferred to our hospital for further treatment.

An abdominal ultrasound was repeated, which confirmed the findings on the CT scan. In addition, the slightly enlarged right ovary showed normal vascularization. Peritoneal fluid (ascites) was increased and was present in the upper and lower abdomen. No abnormalities were seen in the right inguinal region. A pregnancy test was negative. Cultures of blood, vaginal and abdominal fluid were taken. With the differential diagnosis of an acute adnexitis, the antibiotic regime was switched to cefuroxime 750 mg four times daily, metronidazole 500 mg three times daily, and ciprofloxacin 400 mg twice daily, while awaiting culture results. The patient also received hydrocortisone 100 mg three times daily. Our patient's condition deteriorated rapidly and progressed within hours to a state of multi-organ failure comprising circulatory failure, acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), coagulopathy (including thrombocytopenia), and lactic acidosis. A pulmonary artery catheter (PAC) was inserted showing a central venous pressure (CVP) of 19 mmH_2O, cardiac output 8.0 l/min, ejection fraction 33%, wedge pressure 21 mmH_2O, and a central venous blood saturation ($S_{CV}O_2$) of 75%. Chest X-ray showed bilateral pulmonary consolidations consistent with ARDS. Because of the high CVP, an esophageal echocardiography was performed, showing no abnormalities. An explorative laparotomy was performed and showed no abnormalities apart from the ascites. Analysis of the ascites revealed 0.7×10^9/l leukocytes and 0.6×10^9/l polymorphonuclear cells, indicating reactive peritonitis. The blood culture showed Lancefield group A β-hemolytic streptococci (GAS). The antibiotic regime was narrowed to benzyl penicillin 2 million IU six times daily and clindamycin 600 mg three times daily. Intravenous immunoglobulins (IVIG; three consecutive days at 1 g/kg of body weight on day 1 and 0.5 g/kg on days 2 and 3) were administered.

The patient made an excellent recovery and was admitted to our ICU for 8 days, of which she was intubated for 6 days. Several days following admission, mild desquamation of both feet was

Table 2
Overview of published articles on GAS primary peritonitis

Author, year	Age	Sex	Pain in extremity	Diarrhea	Signs of peritonitis	Rash/ desquamation	Imaging	Leukocyte count	Medical history	Surgery	Possible focus	Children ill?	Cultures	Antibiotics	IgG
Graham et al. 1995 [14]	39	F	No	Yes	Yes	Rash + erythema nodosum	Chest-X + X-abdomen: no abnormalities	Leukocytosis, anemia	Not relevant	Laparotomy: ascites	Aerosol?	Yes, pharyngitis	Perineum: GAS (T3/M3/R3)	Cefotaxime + metronidazole → benzyl penicillin → amoxicillin	No
Moskovitz et al. 2000 [15]	39	F	?	Yes	Yes	?	?	Leukocytosis	Not relevant	Yes, not specified. Peritonitis: scant cloudy peritoneal fluid. Appendix mildly inflamed	Aerosol?	Yes, pharyngitis	Blood: GAS; Gram stain peritoneal fluid: rare Gram-positive cocci; vaginal swab: GAS	Levofloxacin + metronidazole → ceftriaxone + sulbactam sodium/ampicillin sodium	?
Vuilleumier and Halkic 2001 [17]	33	F	?	Yes	Yes	?	?	Leukopenia	2 months post-partum	Laparotomy: pus + mild hyperemia of the fimbriae	Genital tract?	?	Peritoneal, endometrium and blood: GAS	Imipenem → clindamycin + meropenem	Yes
Gavala et al. 2002 [18]	40	M	Yes	No	Yes	Erythema	CT-abdomen: peritoneal and extra-peritoneal fluid collections	'Lab signs of inflammation'	?	Laparotomy (2×)	?	?	Pus peritoneum: GAS + *E. coli*	Metronidazole + netilmicin + tazocin	No
Kanetake et al. 2004 [20]	40	M	Yes	Yes	Yes	Rash + erythema + desquamation	X-abdomen: dilated small bowel loops, no free air, confirmed by CT-abdomen and US	Leukopenia	?	Laparotomy: ascites	Aerosol?	Yes, pharyngitis	Ascites: GAS (T-type 22)	Yes, but not specified	Yes
Brivet et al. 2005 [24]	58	F	?	?	Yes	Lumbar rash	CT-abdomen: minimal bilateral pleural and intraperitoneal effusions	?	Appendectomy, salpingitis, miscarriages	Laparoscopy: peritonitis	?	?	Blood: GAS	Amoxicillin–clavulanic acid + gentamicin	No
Brivet et al. 2005 [24]	82	F	?	Yes	Yes	?	Chest-X: bilateral pleural effusion + mass of the right lung. Abdominal-CT: mild intraperitoneal effusion	Leukocytosis, anemia	Epilepsy, colorectal villous adenomas, progressive weight loss, heavy tobacco exposure, and tooth abscess 12 days before admission	No	?	?	Blood: GAS	Amoxicillin–clavulanic acid	No
Saha et al. 2006 [21]	23	F	No	Yes	Yes	No	CT abdomen + US: tubo-ovarian abscess with free fluid	Normal leukocyte count	Not relevant	Laparotomy: ascites + inflamed fallopian tubes; *no* abscess	?	?	Blood: GAS	Ceftriaxone + metronidazole + oral doxycycline → penicillin + clindamycin + ciprofloxacin + doxycycline	No
van Lelyveld-Haas et al. 2008 [22]	28	F	No	No	No	No	?	Leukocytosis	Not relevant	Laparotomy: pus	?	?	Peritoneal pus: GAS; blood: GAS; vaginal swab: GAS	Tazocin → benzyl penicillin	?
Van Den Bossche et al. 2008 [23]	52	F	?	Yes	Yes	Rash/ desquamation	CT-abdomen: free fluid, no signs of perforation	Leukocytosis	'Acute laryngitis' a few days prior to admission	Laparotomy: pus	Larynx?	?	Peritoneal pus: GAS; blood: GAS	Yes, penicillin, erythromycin and clindamycin? (not further specified)	Yes

GAS, group A Streptococcus; X, X-ray; CT, computed tomography; US, ultrasound.

observed. All family members were treated with prophylactic clindamycin for 7 days.

3. Discussion

Most of the described cases of STSS have occurred in association with prior disease and procedures like child birth, skin infections, or surgical interventions.[5–10] Only a few cases of STSS in previously healthy adults have been described presenting as a primary peritonitis in which the source of the GAS infection remained unknown. Some are briefly reviewed here (Table 2).[11–24]

Our patient presented with flu-like symptoms, diarrhea, and severe pain in the right inner thigh with a positive psoas sign. Diagnosis was difficult, as a gynecological cause was suspected, based on the ultrasound findings of an enlarged and painful right adnexal region. An urgent laparotomy was performed and revealed massive purulent ascites without other abnormalities.

Diagnosis of GAS primary or secondary peritonitis can be difficult. It is first important to determine whether the sepsis is a result of a surgical cause (e.g. perforation, ischemia, bowel obstruction, etc.) or not. Brivet et al. advocated that an abdominal CT scan is a sensitive diagnostic tool that can avoid unnecessary laparoscopies: when no convincing abnormalities are found on abdominal CT scan, a conservative supportive approach can be relied upon.[24] However, Farooq and Ammori described a patient with primary bacterial peritonitis diagnosed at laparoscopy and claimed that laparoscopy could well be used as a diagnostic tool in the management of generalized peritonitis.[25] Preference for laparoscopy or laparotomy should be established on an individual basis. We chose laparotomy because of a suspicion of a pathology primarily located in the right psoas muscle or adnexal region.

Analyzing the case reports of primary peritonitis (Table 2) caused by GAS, one can see a clear preponderance of females in the age category 30–40 years, and an association between the female genital tract and a possible bacterial translocation has therefore been speculated.[15,17] Findings on CT scan of a thickened right psoas muscle and adnexal region in our patient may support the hypothesis of bacterial translocation through the female genital tract. The painful right thigh could be explained by the inflammatory reaction of the right psoas muscle (with thickening on CT scan) in the direct surrounding of the right adnexal region, which was possibly the primary site of bacterial translocation and growth.

Severe pain in a lower extremity was also noted in the cases described by Gavala et al.[18] and Kanetake et al.[20] However, the sensitivity and specificity of severe pain in an extremity is difficult to determine, since this has not been described in several case reports. Interestingly, as in our case, some authors noted that the children of the patient had suffered some form of pharyngitis prior to or at the time that the patient had developed symptoms.[14,15,20] The possible source of entry in our patient remains speculative, but could be related to the onychomycosis or the pharyngitis of her children.

In contrast to several other patients who presented with leukocytosis, our patient presented with leukocytopenia. Leukocytopenia was also noted in the cases of Kanetake et al.[20] and Vuilleumier and Halkic.[17] The explanation for this is not clear, but it could be speculated that this is related to the strain involved and the toxin/cytokine profile. Anemia with elevated bilirubin was probably related to hemolysis caused by bacterial hemolytic enzymes. Thrombocytopenia might well be explained by the occurrence of disseminated intravascular coagulation (DIC), which frequently occurs in severe sepsis. In addition, Shannon et al. hypothesized that the M1 protein of *S. pyogenes* triggers immune-mediated platelet (IgG) activation and thrombus formation.[26] Most cases had no relevant medical history and had undergone an abdominal CT and surgical intervention (diagnostic laparotomy) after being treated with broad-spectrum antibiotics. Analyzing the cases in Table 2, it could be cautiously concluded that there is currently no consensus regarding the diagnostic approach and treatment (antibiotics). We used a combination therapy of clindamycin and penicillin, not because of synergistic effects. There is evidence that clindamycin is more effective than penicillin, but penicillin is added to overcome the small possible risk of clindamycin-resistant strains.[27]

In our patient, the GAS infection was confirmed by positive blood culture. Culture of ascites, taken after antimicrobial therapy had been administered, remained negative. Together with the above-mentioned clinical symptoms and laboratory results, our patient fulfilled the proposed criteria for STSS.[28]

We administered high dose steroids, since severe STSS can be associated with lethal bilateral adrenal hemorrhage (Waterhouse–Friderichsen syndrome).[29]

Evidence for the use of IVIG in the management of STSS is scarce, and since it is a rare disease, it has been difficult to conduct a randomized controlled trial. Kaul et al. compared 21 patients with STSS who received 2 g IVIG/kg (single dose) with 32 control STSS patients. Though not randomized and therefore bias-sensitive, the authors concluded carefully that mortality after 30 days was significantly lower in the IVIG group. Furthermore, IVIG therapy enhanced the ability of patient plasma to neutralize bacterial mitogenicity and reduced T-cell production of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).[30] Darenberg et al. performed a multicenter, double-blind, placebo-controlled trial with IVIG in STSS patients. However, because of slow patient recruitment the trial was terminated prematurely. In total, only 21 patients (10 IVIG versus 11 placebo patients) were analyzed. IVIG was provided intravenously for three consecutive days at 1 g/kg of body weight on day 1 and 0.5 g/kg on days 2 and 3. A significant decrease in the sepsis-related organ failure assessment (SOFA) score at days 2 and 3 was noted in the IVIG group.[31] Norrby-Teglund et al. reviewed the use of IVIG in severe GAS infections. Available data suggest that IVIG is probably effective against GAS strains of varying serotypes and with different superantigen production. Potential mechanisms of IVIG are probably related to increased phagocytosis (via opsonizing anti-M antibodies), neutralization of exotoxins (superantigens), and suppression of pro-inflammatory responses.[32]

To summarize, the current best practice treatment of STSS is probably a combination of supportive therapy (fluids, inotropes, vasopressors), clindamycin/penicillin, and IVIG. In addition, corticosteroids and drotrecogin-alpha (recombinant activated protein C) can be administered.

Conflict of interest: No conflict of interest to declare.

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