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Case Report

Two Case Reports of Liver Cirrhosis Complicated by Serious Hemolytic Streptococcal Infection

Hiroshi MATSUDAIRA[1,2], Tomokazu MATSUURA[2,3], Shuji ITO[2], Shinichiro UETAKE[2], Tomoya SASAKI[1,2], Hiroyasu YAMAMOTO[1], Hisato NAKAJIMA[2], and Hisao TAJIRI[2]

[1]*Department of Internal Medicine, Atsugi City Hospital*
[2]*Division of Gastroenterology and Hepatology, Department of Internal Medicine, The Jikei University School of Medicine*
[3]*Department of Laboratory Medicine, The Jikei University School of Medicine*

ABSTRACT

We report two cases (a 67-year-old male and a 76-year-old female), both of whom were followed at the outpatient clinic of our division, primarily for liver cirrhosis. In both cases, following emergency admission for the chief complaint of pyrexia, culture tests detected *Streptococcus pyogenes* and Group B streptococcus, respectively, suggesting the strong involvement of infection in the pathology. Both patients exhibited serious pathology and an increased susceptibility to infection due to their underlying liver disease that seemed to have allowed an infection by indigenous bacteria to be exacerbated. When a patient like this presents with a high fever and a precipitous course of illness, it is important to consider infection caused by indigenous bacteria, such as hemolytic streptococci, when making the diagnosis and to immediately commence treatment with appropriate antibiotics.

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Key words : liver cirrhosis, *S. pyogenes,* fulminant group A hemolytic streptococcal infection, TSLS, group B hemolytic streptococcus

INTRODUCTION

Fulminant group A hemolytic streptococcal infection has an abrupt onset as a result of infection by group A hemolytic streptococci (*Streptococcus pyogenes*). It involves a state of septic shock that rapidly progresses to multiple organ failure (MOF) and has a very high mortality rate[1]. Group B hemolytic streptococcus (GBS) is a pathogenic bacterium that causes infantile meningitis, pneumonia, etc. Although both are present as indigenous flora in the bodies of healthy adults, they have been reported to occasionally give rise to serious pathology. We encountered two patients with infections caused by hemolytic streptococci as a complication of liver cirrhosis who exhibited a variety of clinical manifestations and in whom the infections became exacerbated. Herein, we report these two cases and discuss the pertinent literatures.

CASE REPORTS

Case 1

A 67-year-old male developed a sore throat four days before admission. Clarithromycin and non-steroidal anti-inflammatory drugs were prescribed ; however, he gradually began to feel postprandial pain, and his body temperature increased. He underwent an emergency examination.

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松平　浩，松浦　知和，伊藤　周二，上竹慎一郎，佐々木知也，山本　裕康，中島　尚登，田尻　久雄
Mailing address : Hiroshi MATSUDAIRA, Department of Internal Medicine, Atsugi City Hospital, 1-16-36 Mizuhiki, Atsugi-shi, Kanagawa 243-0004, Japan.
E-mail : hi-matz48@jikei.ac.jp

Despite the administration of ciprofloxacin hydrochloride, his condition failed to improve, and he was admitted the next day. He had been followed since 1993 for diabetes. On intensive insulin therapy, his HbA1c level was maintained around 6.0%. In 1996, he was found to have alcoholic (non-B, non-C) liver cirrhosis. In 2005, he underwent transcatheter hepatic arterial chemoembolization therapy for hepatocellular carcinoma of an S4/8 lesion.

His body temperature was 39.4°C, blood pressure was 124/70 mmHg, and heart rate was 120 beats/min. An examination of the abdomen revealed marked tenderness and rebound tenderness over the entire abdomen. There were no skin manifestations. His laboratory findings are shown in Table 1. Laboratory tests revealed an inflammatory reaction and coagulopathy, but biochemistry tests of liver function showed no marked changes from the observations of the patient's course at the outpatient clinic.

After admission, diagnostic imaging revealed the rapid accumulation of ascitic and pleural fluid (Figs. 1 and 2). Abdominal paracentesis was performed and yielded blood-tinged and very turbid ascitic fluid. The presence of spontaneous bacterial peritonitis (SBP) was therefore suspected. On hospital day 2, we received a report that the Gram-positive bacterium *S. pyogenes* had been detected in the sputum, blood, and ascites cultures performed on admission. We therefore initiated the administration of sulbactam/ampicillin at a dose of 6 g/day. However, the patient's general status rapidly worsened, and he died on hospital day 3. At a later date, it was reported that an analysis of the blood culture performed on admission was positive for streptococcal pyogenic exotoxins (SPEs) A, B, and F.

Table 1. Laboratory findings on admission of Case 1

Hematology	
WBC	2,400/μl (Neutro. 84.4%)
RBC	288×10^4/μl
Hb	9.3 g/dl
HT	28.8%
Plt	3.7×10^4 /μl
Coagulation	
PT	48%
Fbg	353 mg/dl
FDP	36 μg/ml
Biochemistry	
AST	40 IU/l
ALT	24 IU/l
LDH	270 IU/l
ChE	2,058 IU/l
T-Bil	1.6 mg/dl
ALP	148 IU/l
γ-GTP	71 IU/l
TP	5.6 g/dl
Alb	2.5 g/dl
AMY	41 IU/ml
BUN	41 mg/dl
Cr	2.1 mg/dl
UA	7.6 mg/dl
Na	134 mmol/l
K	4.7 mmol/l
Cl	102 mmol/l
NH_3	61 mg/dl
CRP	11.5 mg/dl
FPG	105 mg/dl
HbA1c	6.5%
PIVKA-II	19 mAU/ml
AFP	47 ng/ml

WBC : White blood cells ; Hb : Hemoglobin ; Plt : Platelets ; PT : Prothrombin time ; Fbg : Fibrinogen ; FDP : Fibrin degradation product ; AST : Aspartate aminotransferase ; ALT : Glutammate pyruvate transaminase ; LDH : Lactate dehydrogenase ; ChE : Cholinesterase ; T-Bil : Total bilirubin ; ALP : Alkaline phosphatase ; γ-GTP : γ-glutamiyl transferase ; TP : Total protein ; Alb : Albumin ; BUN : Blood urea nitrogen ; Cr : Creatinine ; NH_3 : Ammonia ; CRP : C-reactive protein ; FPG : Fasting plasma glucose ; HbA1c : Hemoglobin A1c ; PIVKA-II : Des-γ-carboxy prothrombin ; AFP : α-fetoprotein

Case 2

A 76-year-old female began to experience low back pain two days before admission. The pain gradually became accompanied by fever, left eye swelling, and decreased visual acuity. The patient felt weak and was brought to our hospital by ambulance. A hematological examination revealed a severe inflammatory reaction, and the patient was admitted. Since 1993, the patient had been followed for type C liver cirrhosis at the outpatient clinic of our hospital.

Her body temperature was 37.8°C. Left eye swelling was observed. Physical examination revealed no other specific findings. Her laboratory findings are shown in Table 2. No marked changes in liver damage due to the known liver cirrhosis were observed in comparison with the observations of the patient's course at the outpatient clinic ; however, the white blood cell (WBC) count and C-reactive protein (CRP) level were high, suggesting the

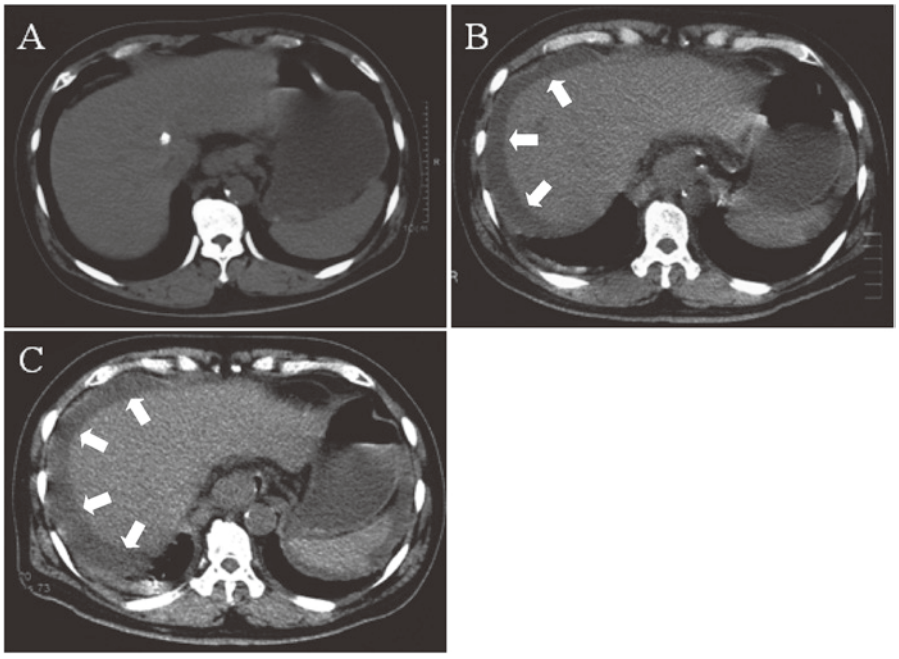

Fig. 1. Computed tomography of the abdomen (A : on admission, B : 11 h later, C : 21 h later)
Ascites (arrows) increased over time. Turbid ascites suggested the presence of SBP.

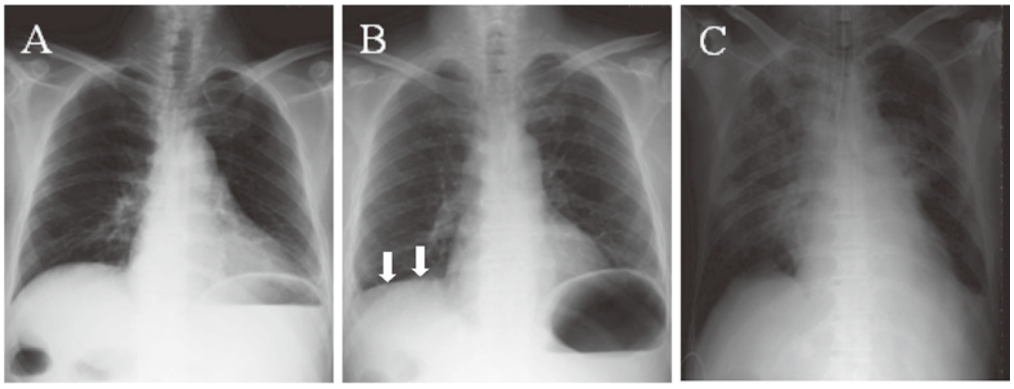

Fig. 2. Chest X-ray
Chest X-ray was taken on admission (A). Pleural effusion (arrows) was observed in the right lung 7 h after admission (B). Right pleural effusion disappeared with respiratory management, but the patient appeared to have developed ARDS 47 h later (C).

presence of severe inflammation.

We initiated treatment with meropenem hydrate (MEPM) at a dose of 1 g/day on admission to treat an infection of unknown origin. Various diagnostic imaging studies also failed to reveal any findings that suggested the cause of the infection or consciousness disorder. An examination performed by an ophthalmologist on hospital day 2 to evaluate the left eye swelling and pain revealed hyphema and opacity, while magnetic resonance imaging (MRI) of the orbit showed inflammatory changes in the left globe that extended into the muscles in the left orbit and surrounding adipose tissue (Fig. 3).

There were no episodes of trauma or surgery, and a diagnosis of endogenous endophthalmitis was made. GBS was subsequently detected as a result of a blood culture performed on the day of admission that suggested the presence of endogenous bacterial endophthalmitis and sepsis. The antibiotic regimen was switched from MEPM to benzyl penicillin potassium (PCG ; 18,000,000 units/day) on hospital day 7, and the inflammatory reaction rapidly im-

Table 2. Laboratory findings on admission of Case 2

Hematology	
WBC	12,100/μl (Neutro. 93.5%)
RBC	424×10^4/μl
Hb	14.2 g/dl
HT	40.8%
Plt	4.0×10^4/μl
Coagulation	
PT	86%
Fbg	872 mg/dl
FDP	33 μg/ml
Biochemistry	
AST	105 IU/l
ALT	63 IU/l
LDH	334 IU/l
ChE	1,564 IU/l
T-Bil	1.4 mg/dl
ALP	219 IU/l
γ-GTP	56 IU/l
TP	6.9 g/dl
Alb	3.1 g/dl
AMY	41 IU/ml
BUN	48 mg/dl
Cr	0.8 mg/dl
UA	5.6 mg/dl
Na	138 mmol/l
K	4.4 mmol/l
Cl	103 mmol/l
NH_3	60 mg/dl
CRP	13.5 mg/dl
FPG	126 mg/dl
HbA1c	4.8%
PIVKA-II	89.0 mAU/ml
AFP	5 ng/ml

proved. However, despite treatment with antibiotic eye drops, including gentamicin sulfate, the decreased visual acuity of the left eye was irreversible, and the patient's light-sense was ultimately lost. The patient was discharged on hospital day 56.

DISCUSSION

Fulminant-type group A hemolytic streptococcal infection involves a state of septic shock with an abrupt onset caused by *S. pyogenes* that rapidly progresses to MOF[1]. Because it exhibits a pathology that resembles the toxic shock syndrome (TSS) of *Staphylococcus aureus* infections, it is called toxic shock-like syndrome (TSLS) or streptococcal TSS (STSS). TSLS was first reported in Japan in 1993, and, since then, approximately 40 cases have been reported annually[2]. Approximately 40% of affected patients die, as TSLS is an infection with an extremely high mortality rate. The age of onset is higher than that observed in other hemolytic streptococcal infections, and, in many cases, the infection develops suddeenly in otherwise healthy adults[3]. In a survey conducted by Igarashi et al., 11.9% of TSLS patients had a history of liver dysfunction, followed by 10.3% with a history of hypertension and 7.9% with a history of diabetes[4]. However, patients with no underlying diseases accounted for the largest group, 27.0%. The initial symptoms are limb pain, swelling, fever and low blood pressure, and the progression of the illness after onset is very rapid and dramatic. Within several tens of hours after onset, the disease causes soft tissue necrosis, acute renal failure, adult respiratory distress syndrome (ARDS),

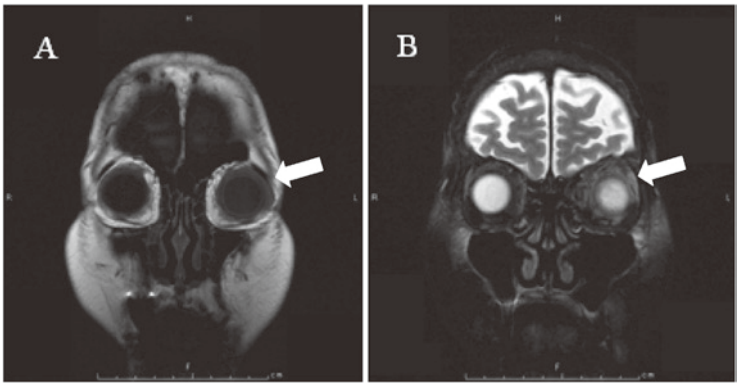

Fig. 3. MRI of the orbit (A ; T1 weighted image, B ; T2 weighted image)
Inflammatory change in the left globe that extended into the muscles in the left orbit and surrounding adipose tissue (arrows).

disseminated intravascular coagulation (DIC) and MOF and, in many cases, death from shock[5]. The impression that soft tissue rapidly becomes necrotic and results in death is the reason why the bacteria have been taken up by the media as "flesh-eating bacteria" and have become a topic of conversation. Although no skin manifestations were observed in Case 1, the patient met the diagnostic criteria proposed by the United States Centers for Disease Control and Prevention (CDC) in 1993 and was diagnosed with TSLS[6].

Intensive antibacterial therapy consisting of the administration of three- to four-times the usual dose of the penicillin of first choice is necessary to treat TSLS. Moreover, in serious septic states, clindamycin which exhibits high tissue penetration is recommended[7]. In addition, there are reports that the administration of large doses of immune globulins are effective as neutralizing antibodies against exotoxins[8,9]. In Japan, Imamura et al. have shown that, based on inhibition of the TSS-like cytokine storm caused by the SPE that is often detected in TSLS patients and the mechanism that removes endorphins, endotoxin adsorption therapy is effective against TSLS that develops in patients with primary peritonitis[10]. In addition, a report by Matsumura et al. showed that continuous hemodiafiltration with a polymethylmethacrylate membrane hemofilter performed in two simultaneous series was life-saving for treating TSLS with SBP as the source of infection in a patient with primary sclerosing cholangitis and liver cirrhosis[11]. These were also treatment options in Case 1, in which the patient was positive for SPE A, B, and F exotoxins, which exhibit superantigen activity and release large amounts of cytokines in response to reactions with T-cell receptors[12].

GBS has been isolated from female genitalia and the digestive tract and is known to be a pathogenic bacterium that causes neonatal sepsis, meningitis, and pneumonia. Recently, there has been an increase in the number of reports in which pathogenicity is observed in adult males with chronic diseases[13,14]. In addition, endophthalmitis is thought to be common in patients with underlying diseases, such as diabetes or malignant tumors. This condition is classified as either endogenous, in which the bacteria infect the inside of the globe hematogenously from a primary source within the body, or exogenous, in which onset occurs after trauma, eye surgery, etc. Endogenous bacterial endophthalmitis is thought to be a relatively rare disease that accounts for only approximately 5% of cases of endophthalmitis[15]. Moreover, even among that 5%, as far as the authors were able to determine in a search of the Japan Medical Abstracts Society (Ichushi) database for previous reports of endogenous endophthalmitis caused by GBS in Japan using the key words "endophthalmitis" and "*Streptococcus agalactiae*" or "GBS" or "endogenous endophthalmitis" and "*Streptococcus agalactiae*" or "GBS," there have only been nine cases reported in Japan, including our own cases and excluding society proceedings. Among these nine cases, diabetes was an underlying disease in four ; our Case 2 was the only one in which GBS endophthalmitis occurred as a complication of liver damage[16-24]. In a report by Mandell et al., 30% of 271 patients with GBS infections had diabetes as an underlying disease, followed by liver failure in 24%, neurologic diseases in 21%, and malignant tumors in 19%[25].

The use of PCG monotherapy is recommended as soon as the diagnosis of GBS infection is made, although GBS is also thought to be sensitive to vancomycin hydrochloride and first- to third-generation cephalosporins[25]. In Case 2, when the antibiotic regimen was switched to large-dose PCG as soon as the pathogenic bacterium was identified, although the decrease in the visual acuity of the left eye was irreversible, a tendency toward improvement was observed with respect to the patient's inflammatory reaction and general condition.

Abundant immunocompetent cells are present in the liver, particularly in the sinusoids. Because these cells maintain a balance between the immune response and immune tolerance, immune functions related to endogenous and exogenous antigens are thought to be disrupted by liver injury[26,27]. Kupffer cells, which are a type of cell present in sinusoidal cells, play a role in the body's defenses by phagocytizing foreign bodies that flow into the liver. Impairment of the phagocytic capacity of Kupffer cells not only means that Kupffer cells cannot phagocytize foreign cells and their components that flow into the liver, but also indicates that endotoxins and other toxic substances can flow into the liver[26,27]. Moreover, chemical substances, such as cytokines and chemokines, are overproduced by Kupffer cells, thereby causing a worsening of the liver damage. When portosystemic shunts form, the bacteria and their toxic substances, such as endotoxins, fail to be removed by the liver and flow into the entire body[28]. Moreover, as a result of liver

injury, abnormalities occur in important implementers of the immune functions produced in the liver, such as immune globulins and complements, which accelerates liver damage[29,30].

In conclusion, for the aforementioned reasons, patients who present with liver damage are considered to be in a constant state of increased susceptibility to infection, and fatal outcomes have been reported, even in patients with infections caused by pathogenic bacteria with low pathogenicity[31]. In both of the present cases, differences in the etiology and stages of liver damage were seen, and the impact of diabetes must also be considered to a large extent in Case 1. However, the fact that hemolytic streptococci, which usually exhibit a low degree of pathogenicity, caused a severe infection was common to both cases, and sufficient caution is necessary clinically. Shirai et al. reported a case of TSLS that developed as a result of a mucosal biopsy during upper gastrointestinal endoscopy in a patient with diabetes as the underlying disease[32]. It is also necessary to realize that this disease may develop as a result of examination of the digestive organs.

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