CASE REPORT

Massive haemolysis, gas-forming liver abscess and sepsis due to *Clostridium perfringens* bacteraemia

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SUMMARY

Clostridial soft tissue infections are infrequent, but can be life-threatening when associated with certain underlying conditions, such as immunosuppression or malignancy. When bacteraemia occurs, it can be accompanied by haemolysis. Only surgical removal of the focus of infection and early onset of antibiotic therapy can prevent a very poor outcome. We describe the case of a man aged 65 years who presented with sepsis, haemolysis and rapid worsening. The identification of a gas-forming liver abscess, the early percutaneous drainage and the prompt initiation of antibiotic treatment were the key factors in the outcome of this patient.

BACKGROUND

Clostridium perfringens is an anaerobic, Gram-positive, rod-shaped, bacteria that can be found in the human gastrointestinal tract and genitourinary tract in healthy patients. When certain underlying conditions are present, *Clostridium* species may become pathogenic and be the causative agent of soft tissue, bloodstream and gas-forming infections, which can result in significant mortality.^{1 2} Fortunately, only 0.5–2% of positive blood cultures are due to clostridial species, and among them, *C. perfringens* is the most frequent isolation (20–50%),³ followed by *Clostridium septicum* (19.6%), *Clostridium clostridioforme* (15%) and *Clostridium tertium* (10.9%).¹

Several cases have been reported on severe *C. perfringens* infections and gas-forming abscesses, and several case studies have been published on the topic, emphasising the high level of mortality and the difficulty in identifying the clinical features that would lead clinicians to promptly establish a diagnosis in the early stages.⁴

CASE PRESENTATION

A man aged 65 years was admitted to our hospital presenting with a 3 hour history of epigastric pain, fever, chills and decreased alertness. He was stuporous and was not able to describe further symptoms. He had a medical history of type 2 diabetes and syringomyelia due to a Chiari type I malformation (he was asymptomatic). The patient was on insulin glargine, insulin glulisine, sitagliptin and metformin.

At the time of assessment, the patient appeared confused and had a temperature of 37.8°C, heart rate of 115 bpm, blood pressure of 134/73 mm Hg and oxygen saturation of 92% on room air. On

auscultation, heart and breath sounds were normal. The abdomen was soft and there was no hepatomegaly.

Blood tests revealed a white cell count of 22 210/μL, with 83% neutrophils, a haemoglobin level of 14.6 g/dL and a platelet count of 168 000/μL. Lactic acidosis and raised inflammatory markers were found: pH 7.37, pCO₂ 23.5 mm Hg, HCO₃ 17 mmol/L, arterial lactate 3.10 mmol/L (normal range: 0.5–1.6 mmol/L) and C reactive protein level of 96 mg/dL (normal range: <5 mg/dL).

Since the patient was stuporous, it was decided to perform a lumbar puncture in order to obtain a sample of cerebrospinal fluid (CSF). The brain CT performed prior to the lumbar puncture was normal, except for the already known syringomyelia. The CSF showed a glucose level of 165 mg/dL and protein level of 44 mg/dL (normal range 10–45 mg/dL) and white cell count of 8/μL. Although meningitis had been reasonably ruled out, we decided to initiate empirical treatment with ceftriaxone 2 g daily and levofloxacin 500 mg daily.

By the time the patient was admitted to the hospitalisation ward, his blood pressure was 105/60 and respiratory rate was 24 breaths/min. His alertness decreased and he was admitted to the intensive care unit (ICU). The laboratory findings revealed a marked worsening, with a white cell count of 29 000/μL, with 91% neutrophils, a haemoglobin level of 12.6 g/dL, C reactive protein level of 409 mg/dL (normal range: <5 mg/dL), alanine transaminase (ALT/GPT) level of 402 IU/L and gamma-glutamyl transferase level of 268 IU/L. The analytical evolution is shown in [table 1](#).

The most remarkable findings were anaemia, which was not present at the time of admission, the elevated LDH levels and the presence of schistocytes and ghost cells on the peripheral blood smear, which led us to consider haemolysis. The direct Coombs test was negative. Despite the haemolytic anaemia, the patient did not need a blood transfusion.

INVESTIGATIONS

While in the ICU ward, an abdominal ultrasound was performed. It revealed a 5 cm low-density area with gas formation in the right inferior-posterior subsegment of the liver. The abdominal CT showed a lesion in the right lobe measuring 4.5×4.3×4.8 cm ([figures 1 and 2](#)). A diagnosis of gas-forming liver abscess was therefore established. The antibiotic therapy was then replaced by meropenem 1 g intravenous every 8 hours and

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Table 1 Course of the laboratory data

	On admission	+10 hours	+17 hours	+20 hours (drainage)	+44 hours	+68 hours	+82 hours
White cell counts (/μL)	22 210	29 770	25 980	20 620	17 840	17 670	14 140
Haemoglobin (g/dL)	14.6	12.6	10.4	9.8	9.4	9.2	9.6
Platelets (/μL)	168 000	185 000	151 000	148 000	148 000	184 000	205 000
C reactive protein (mg/dL)	96.7	409.3	398.7				
Procalcitonin (ng/mL)				31.3	11.79	5.55	2.74
Arterial lactate (mmol/L)		3.10		2.20	1.44		1.11
Bilirubin (mg/dL)		2.6		0.9			0.4
GGT (IU/L)		268		279			254
GPT/ALT (IU/L)		402		310			53
LDH (IU/L)				1237			373
Peripheral blood smear		Schistocytes, ghost cells					
Antibiotic treatment	Ceftriaxone+levofloxacin	Meropenem+metronidazole					
Hospitalisation ward		Intensive care unit					
Before percutaneous drainage		After percutaneous drainage					

Procedures are also shown.

Figure 1 Sagittal plane (A) and coronal plane (B) showing the liver abscess with gas formation (arrows).

Figure 2 A CT showing the liver abscess in the right lobe of the liver (white arrow).

metronidazole 500 mg intravenous every 8 hours. A CT-guided percutaneous drainage was performed. A few hours after the procedure, blood cultures revealed *Escherichia coli* and *Clostridium perfringens*, which were also positive in the sample

obtained after the drainage. Both bacteria were sensitive to metronidazole, meropenem and piperacillin/tazobactam.

OUTCOME AND FOLLOW-UP

After the percutaneous trans-hepatic drainage, the patient significantly improved. He remained on the ICU ward for 4 days and was then transferred to the hospitalisation ward (Internal Medicine department). The patient underwent a gastroscopy and a colonoscopy, both of which were normal. He was on antibiotic therapy for 6 weeks. Another abdominal CT at the time of discharge showed that the liver abscess had resolved. The patient was discharged in a stable condition, with no antibiotic treatment.

DISCUSSION

Clostridial infections are responsible for a wide range of infections, such as bacteraemia, gastroenteritis, wound-associated gangrene, gas-forming abscesses in the soft tissue, necrotising enteritis, fatal acute haemolysis and shock.¹ Bacteraemia due to *C. perfringens* is uncommon, but often associated with a fatal outcome.^{1 4} Sepsis due to *Clostridium* infections is known to have a poor prognosis, often associated with shock and massive haemolysis.^{4 5} It is generally accepted that identifying the clinical features of *C. perfringens* infections is difficult.

Identifying a pyogenic liver abscess can be also challenging. Although epigastric pain and fever are common features, they are non-specific. Pyogenic liver abscesses are often polymicrobial, and *E. coli* and *Klebsiella pneumoniae* are the two most frequently isolated pathogens.⁶ Mortality is ~15%, but it depends on the underlying cause and the pre-existing hepatic disease.⁷ Broad-spectrum antibiotic therapy, percutaneous or surgical drainage and, if possible, control of the primary source are the main keys to preventing a dramatic outcome. Malignancy, immunosuppression and hepatobiliary disease are often the predisposing conditions to liver abscesses and associated bacteraemia. However, in the work-up that followed, once our patient had remained stable, we did not find any underlying conditions, except for the fact that he was diabetic.

There are five serotypes of *Clostridium perfringens* (A, B, C, D, E), according to the production of four toxins (alpha, beta, epsilon, iota). Alpha-toxin-producing type (type A) is the most common isolation, responsible for gas gangrene and

enterotoxaemia, whereas types B (alpha, beta and epsilon toxin), C (alpha and beta-positive) and D (alpha and epsilon-positive) are responsible for enterotoxaemia in humans and animals. The pathogenicity of type E (alpha and iota-positive) remains unclear, and it is often interpreted as false positives.⁸

Acute massive intravascular haemolysis only occurs in 7–15% of *C. perfringens* bacteraemia, but it is typically the most severe complication, and its outcome is dramatic, with a mortality rate of 70–100%.⁴ This haemolysis is caused by α -toxin, mostly in *C. perfringens* type A, which can disrupt the membrane of the erythrocytes due to phospholipase C activity. Therefore, a peripheral blood smear may show spherocytes, ghost cells and schistocytes, suggesting the presence of haemolysis. In addition to this, bilirubin, potassium and d-lactate dehydrogenase levels can be elevated.

This α -toxin is also regarded as a key pathogenic mechanism in the destruction of soft tissue, and the development of gangrene and gas-forming abscesses. Therefore, a goal in the management should be the minimisation of this toxin, by using proper antibiotics and surgical removal or drainage of the focus of infection.²

Several case studies have been performed in order to study the clinical features, comorbidities and outcomes of severe *C. perfringens* infections, which allow some conclusions to be drawn regarding the course of the infections. Patients typically have an underlying disease, such as immunosuppression, malignancy, liver cirrhosis or diabetes.⁴ Sometimes, a prior invasive procedure in the gastrointestinal, hepatobiliary tract or line insertion⁹ is the key to bloodstream infection.

Early identification of *C. perfringens* infections is difficult, because inflammatory signs are non-specific, and the focus of the infections is not always obvious. According to several publications,^{2 3 4} the focus of infection is hepatobiliary, gastrointestinal or uterine, associated with a soft tissue local infection or after an invasive procedure, as precipitating factors. Surgical removal or drainage of the abscesses have been proven to be a prognostic factor.^{1–4}

Management relies on early identification and removal of the focus, prompt antibiotic treatment and supportive care. Awareness of the acute haemolysis is essential, because it can easily lead to poor prognosis. Since there may be a delay in receiving blood culture results, these measures must be promptly taken. *Clostridium* is usually sensitive to penicillin G, clindamycin, metronidazole, cefoxitin and piperacillin/tazobactam. Clindamycin and metronidazole are regarded as having anti-toxin activity, whereas cephalosporins and penicillins do not have such activity. A therapy based on penicillin plus clindamycin has been demonstrated to reduce the risk of death.²

Our patient received broad-spectrum antibiotic therapy within hours of admission. The liver abscess was promptly identified and properly managed by means of a percutaneous drainage. Since this disease is uncommon, but can be potentially life-threatening, our management probably prevented a rapid deterioration of the patient. We had no suspicion of a liver

abscess, and the former therapy (ceftriaxone and levofloxacin) was empirical, but probably insufficient.⁵ We were only able to properly manage the infection when we noticed the gas-forming abscess.

Learning points

- ▶ *Clostridium perfringens* bacteraemia is an infrequent, life-threatening condition which is difficult to identify. A high clinical suspicion is needed to establish an early diagnosis of septicaemia due to this pathogen. Only blood cultures and gas-forming lesions spotted by imaging studies can identify clostridial infections.
- ▶ When suspected, early onset of antibiotic therapy and surgical or percutaneous removal of the abscess are the key to preventing a fatal prognosis.
- ▶ The presence of massive haemolysis and shock at presentation are the main prognostic factors, as mortality due to this life-threatening combination is extremely high.
- ▶ Direct examination of peripheral blood smear may demonstrate schistocytes, spherocytes and ghost cells, strongly suggesting intravascular.

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