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Intravascular haemolysis and septicaemia due to *Clostridium perfringens* liver abscess

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SUMMARY

Intravascular haemolysis is a rare but serious complication of Clostridium perfringens sepsis. The outcome is usually fatal unless treatment is started early. We describe a case of survival after haemolysis and multiple organ failure in the setting of a ruptured liver abscess and sepsis caused by C. perfringens in an immunocompetent 58-year-old male.

Key Words: Clostridium perfringens, hepatic abscess, septicaemia, intravascular haemolysis, hyperbaric oxygen therapy

CASE HISTORY

A 58-year-old male presented with a 10-hour history of right-sided loin pain and dark coloured urine. He had no significant past medical history. His temperature was 38°C, pulse rate 78 /minute and blood pressure 130/80 mmHg. He was conscious and fully oriented with no audible heart murmur and a clear chest on auscultation. He had severe tenderness in his right loin with macroscopic haematuria. His haemoglobin was 13.5g/dl, white cell count 14.6×10^9/l, neutrophil count 13.34×10^9/l, platelets 142×10^9/l, sodium 139 mmol/l, urea 9.7 mmol/l, creatinine 165 μmol/l, amylase 170 IU/l and C-reactive protein 52 mg/l. Other biochemical results were unavailable due to haemolysis of the blood sample. Electrocardiogram and chest X-ray were unremarkable. He was admitted to the emergency assessment unit with a clinical diagnosis of pyelonephritis and renal calculi and started on levofloxacin empirically after blood culture sampling. As he was clinically stable, further imaging was planned for the next morning. However, severe sepsis and acute renal failure with anuria supervened within a few hours of admission and he was referred to our intensive care unit. His condition deteriorated very rapidly, requiring ventilation and large doses of inotropes. Further repeat blood samples showed a decreased haemoglobin (9 g/dl) and low haematocrit (0.255) with gross haemolysis. A peripheral film revealed numerous spherocytes with haemolysed plasma and direct antiglobulin test was negative, leading to a suspicion of clostridial infection. Intravenous antibiotic therapy was changed to benzylpenicillin, clindamycin and metronidazole. Blood culture obtained initially during his admission confirmed *Clostridium perfringens* within two hours of incubation.

We screened the patient in search of a source of the organism. Plain X-ray of the abdomen showed a suspicious gas-containing space in the region of the right lobe of the liver (Figure 1). Ultrasound of the abdomen was inconclusive. Computerised tomography of the abdomen confirmed a liver abscess and gas collection in the posterior segment of the right hepatic lobe and around the gall bladder (Figure 2). Exchange transfusion (removal of 500 ml of whole blood for each unit of packed red

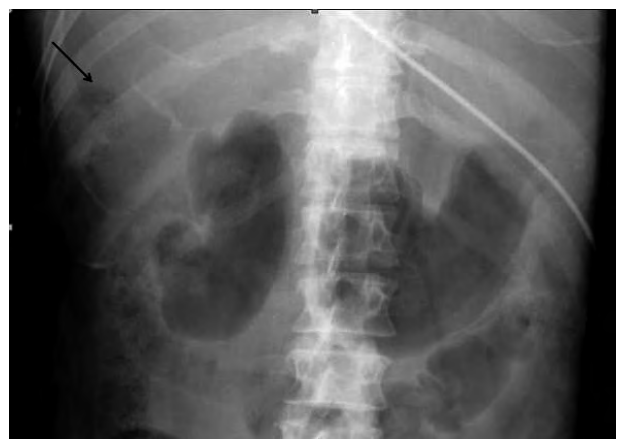

FIGURE 1: Plain X-ray of the abdomen – gas containing lesion in the region of the liver.

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cell transfusion) was initiated for treatment of haemolysis. Despite the cardiovascular instability and haemolysis, he underwent urgent laparotomy for drainage of the liver abscess and cholecystectomy. The laparotomy findings included bile peritonitis with a ruptured liver abscess. Swabs from the intraperitoneal pus and gall bladder also grew *C. perfringens*.

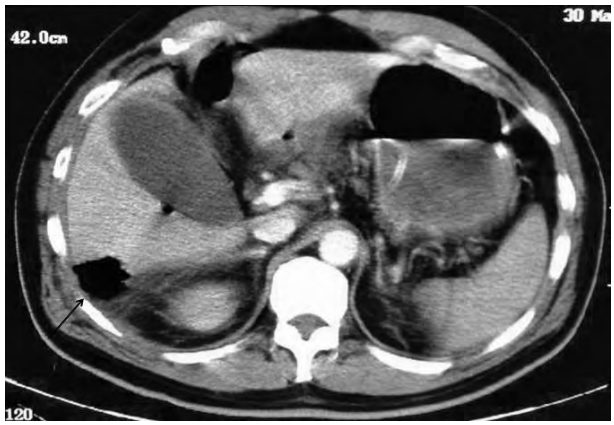

FIGURE 2: Abdominal computed tomography scan – gas filled abscess in the right lobe of the liver.

On the same day following the surgery, he had one session of hyperbaric oxygen therapy (HBOT) – 2.2 atmospheres absolute pressure (ATA) for 120 minutes. He required several days of haemodiafiltration for renal failure. With intensive management, his condition improved gradually. He was successfully weaned and discharged after three weeks. He is now currently well with chronic stable renal dysfunction and serum creatinine of 176 μmol/l.

DISCUSSION

Massive intravascular haemolysis is a classic complication of clostridial sepsis[1] and usually fatal unless treatment is commenced early[2]. Clostridium infections are often associated with genitourinary or gastrointestinal malignancies, acute leukaemia, and secondary to radiation, chemotherapy and embolisation, post-abortal and post-partum infections and rarely of unknown origin[3-7]. A possible source of infection in this patient is bacterial translocation from the gastrointestinal tract seeding distant sites (liver and gall bladder).

C. perfringens is an anaerobic Gram positive spore-forming bacillus that can proliferate in a very short time (doubling time seven minutes)[3]. It is a commensal of human colonic flora and skin. It produces various toxins (at least 12) of which the alpha toxin is very potent. Alpha toxin is a lecithinase which destroys the lipids in the cell membrane causing cell lysis and tissue death. It also produces haemolysis, platelet destruction and widespread capillary damage. This results in reduced blood supply and anaerobic conditions which favour further rapid multiplication of this gas-producing organism[8]. This can cause myonecrosis (gas gangrene) progressing to rapid systemic shock, renal failure, intravascular haemolysis and death in 12 to 24 hours. The incubation period is commonly less than three days but can be less than 24 hours[9-10].

The diagnosis of *C. perfringens* with haemolysis is based on the following:

1. Full blood count may demonstrate anaemia with a raised mean cell haemoglobin concentration and a reduced mean cell volume. Severe haemolysis may be obvious on the visual inspection of the sample. Blood film may demonstrate spherocytosis with fragmentation. Indirect and direct antiglobulin tests (DAT or Coombs) are negative[11,12].
2. Haemoglobinuria or frank haematuria.
3. Gram stain of a peripheral blood smear may show Gram positive rods. This is a rapid test which may confirm the diagnosis[13].
4. Blood or tissue culture[12].
5. Imaging may reveal the presence of any abscess or gas in tissues which may be the source of the sepsis. In this case a routine plain radiograph of the abdomen gave us the valuable lead in identifying the septic focus.

C. perfringens sepsis carries a very high mortality. Rapid diagnosis and aggressive early management is of paramount importance.

Surgical debridement of any probable cause or source is warranted. Benzylpenicillin is the antibiotic of choice and combination with clindamycin is thought to improve survival compared to penicillin alone[9]. Chloramphenicol, doxycycline, imipenem and metronidazole are alternative agents.

Exchange transfusion could be considered at an early stage of intravascular haemolysis to prevent further complications. Low levels of platelets, fibrinogen and Factor VIII indicate consumption of coagulation factors. This could be secondary to release of thromboplastins from platelets and damaged red cells promoting intravascular coagulation. Immediate exchange transfusion could be beneficial by removing these toxin-damaged red cells, free haemoglobins and fibrin split products[14]. In our patient, although at least four to six units of exchange transfusion were planned, only one unit was exchanged. This was because urgent

computerised tomography imaging and emergency surgery took precedence. There was a significant blood loss during surgery and packed red cells and coagulation products were transfused. Hence further exchange transfusion was not carried out.

There are no controlled human trials but several case series and case reports have reported that HBOT contributes to dramatic clinical improvement[15-17]. One experimental study on rats indicated significant improvement in morbidity and mortality when HBOT was combined with surgery[18]. Clostridia lack superoxide dismutase, making them incapable of surviving in the oxygen-rich environment created within a hyperoxic tissue. While tissue oxygen tension (PO_2) is normally between 20 and 40 mmHg on breathing air, it increases to 250 mmHg at 2 ATA oxygen and 450 mmHg at 3 ATA oxygen. At tissue PO_2 of 80 mmHg or greater, *C. perfringens* ceases to produce further toxins[19]. Also, with HBOT peroxides build up and inactivate or kill the anaerobic bacteria. This effect is enhanced by surgical debridement of catalase-liberating necrotic tissues, as catalase could inactivate peroxides.

The suggested dose of HBOT in the literature varies and is often 2 to 3 ATA oxygen for 60 to 120 minutes per session; total number of sessions range from two to 12 with two to three sessions a day[18]. Although multiple HBOT sessions are recommended in the literature, our patient had only one session due to logistic problems and marked improvement in his condition after the first session.

The mortality rate of *C. perfringens* sepsis ranges between 70 and 100%[10]. In most of the *C. perfringens* cases reported in the literature, the diagnosis was confirmed only after death[20-23]. The only survivors were those in whom treatment was initiated before they developed severe haemolysis. As summarised by Alberto Alvarez et al[24], only 19 cases of *C. perfringens*-associated haemolysis were published till 1999 and most of the patients had an extremely rapid illness with death in a few hours. To date, only one published case report has mentioned survival following *C. perfringens* sepsis secondary to liver abscess. That patient had received HBOT[6].

Our patient showed good progress after one session of HBOT. Hyperbaric chambers are available at only selected centres and the risk benefit of transferring a critically ill patient with multi-organ support from intensive care must be assessed in each case.

A high index of suspicion, initiation of appropriate antibiotics without delay, timely surgical intervention, HBOT if available and aggressive supportive care with a multi-disciplinary team approach could result in patient survival in this commonly fatal illness.

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