

Fatal *Clostridium* Septicaemia Associated with Massive Intravascular Haemolysis in a Previously Healthy Woman

Dear Sir,

A 64-year-old Chinese female with a past history of acute cholecystitis treated conservatively with antibiotics first presented with fever, upper respiratory symptoms and mild jaundice. On initial evaluation, the patient was febrile with a temperature of 39.1°C. Other than mild jaundice, physical examination was otherwise unremarkable. In particular, abdominal examination revealed a soft and non-tender abdomen, with no organomegaly, while the lungs were clear on auscultation.

Investigations revealed a haemoglobin of 12.4 g/dL (11.0-15.0), white blood cell count of 39.3 x 10(9)/L (3.6-9.3) with predominantly neutrophilia (93.8%) and platelets of 268 x 10(9)/L (170-420). Renal function was normal. A peripheral blood smear showed a leukoerythroblastic picture. Some spherocytes were seen, with little evidence of microangiopathy. No malarial parasites were seen. Chest radiography showed mild bibasal infiltrates. No free air was noted under the diaphragm. With the clinical history of upper respiratory symptoms and fever, as well as the initial blood film findings of spherocytosis, a presumptive diagnosis of possible atypical pneumonia with immune mediated haemolytic anaemia was made and the patient was started on intravenous ceftazidime and erythromycin. Shortly after her admission to hospital, she developed features of massive intravascular haemolysis. She was noted to have worsening jaundice and haemoglobinuria, and her haemoglobin dropped from her initial Hb: 12.4 g/dL to 8.1 g/dL within 7 hours of admission. In addition, all blood specimens sent after her admission were noted by the laboratory to be haemolysed and the serum was red, which is consistent with marked haemoglobinaemia. The massive haemolysis also interfered with the photometric assays, causing difficulty in assessing her liver function tests (including her bilirubin, aspartate aminotransferase (AST) and lactate dehydrogenase) as well as in the calculation of her red cell indices. Her peripheral blood films done showed a progressive increase in spherocytosis as well as increased polychromasia, and her Direct Coomb's test was negative. She was also noted to have a reticulocytosis of 13.6% [absolute count 312.2 x 10(9)]. Despite changing her antibiotics to meropenem and levofloxacin for broader spectrum coverage, she deteriorated rapidly, developing acidosis and hypoxia. Despite aggressive measures in the intensive care unit, she continued to deteriorate and

succumbed 9 hours after admission. Her blood cultures came back 2 days later positive for *Klebsiella pneumoniae* and *Clostridium perfringens*.

Clostridium perfringens bacteraemia is a rare but known cause of massive intravascular haemolysis and is almost always fatal if untreated. This phenomenon has been classically described in patients with underlying malignancies,¹ those with post-abortal and postpartum infections,² and those who are healthy, but with an underlying portal of entry for bacteria such as liver abscesses, cholecystitis, pneumonia and empyema, gastrointestinal arteriovenous malformations and endocarditis.

The pathogenesis of haemolysis has been attributed to an elaboration of a clostridial toxin, alpha toxin, which is a phospholipase C lecithinase. Alpha toxin hydrolyses sphingomyelin and lecithin to phosphoryl choline and diglyceride, leading to a disruption of cell membranes and causing cell lysis.³ This condition is almost always fatal unless appropriate treatment is commenced early. The definitive treatment consists of appropriate antimicrobial agents as well as surgical debridement of any possible source of infection. In addition, hyperbaric oxygen therapy may be considered in combination with antibiotics and surgery in patients with clostridial associated gas gangrene.⁴ High-dose penicillin is the antimicrobial of choice, although a second agent for broader coverage of mixed infection should be added empirically based on the clinical setting. Second or third generation cephalosporins, clindamycin, metronidazole, chloramphenicol and imipenem are also considered appropriate.⁵

Our case is unusual in that our patient had no underlying predisposing condition and no evident source of her *Clostridium perfringens* infection was found despite an extensive clinical examination. In view of her previous history of cholecystitis, and in view of the growth of *Klebsiella pneumoniae* in addition to *Clostridium* in the blood culture, we speculate whether there could have been an underlying hepatobiliary sepsis. However, no autopsy was done, making this diagnosis difficult.

This case illustrates the importance of considering clostridial septicaemia in any toxic-looking patient with fever, jaundice and evidence of significant intravascular haemolysis even in the absence of an underlying malignancy, or a predisposing lesion. The prompt institution of appropriate antimicrobial therapy might allow the clinical improvement of an otherwise fatal disease.

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