Self-assessment corner

Coma during *Salmonella typhimurium* septicaemia

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A 32-year-old man who had regularly been consuming heroin was admitted with general weakness. Temperature was 37.5°C, pulse, blood pressure and clinical examination were normal except for a painful swelling of the right leg; there were no abdominal complaints. Laboratory findings were: white blood cell count $14.5 \times 10^9/l$, creatinine 171 $\mu\text{mol/l}$, creatine kinase 41 508 IU/l, aspartate transaminase 726 IU/l, alanine transaminase 315 IU/l. Screening for toxins was negative. After obtaining blood for culture, therapy with clavulanate/amoxicillin, amikacin and vancomycin was begun.

The next day, the patient's condition worsened and his temperature rose to 40°C; pulse was 110 beats/min and blood pressure 114/58 mmHg. He became comatose with a Glasgow coma score of 7 and signs of respiratory distress. On examination there was diffuse tenderness of the abdomen. Laboratory findings were: white blood cell count $20.3 \times 10^9/l$, creatinine 292 $\mu\text{mol/l}$, creatine kinase 18 000 IU/l, aspartate transaminase 516 IU/l, alanine transaminase 313 IU/l with early signs of disseminated intravascular coagulation. A Western blot was positive for HIV1, the CD₄-cell count was 191 cells/mm³. Lumbar puncture yielded sterile cerebrospinal fluid (CSF) containing 0.36 g/l of protein, 2.7 mmol/l of glucose and <1 cells. Cryptococcic and HIV antigen, polymerase chain reaction for cytomegalovirus and herpes simplex virus were negative. The trachea was intubated and he was mechanically ventilated. On the third day the Glasgow coma score was 4, plantar responses were flexor, deep tendon reflexes were hyperreactive and there were signs of decerebration. Disseminated intravascular coagulation was becoming more severe. Three blood cultures and one stool culture were positive for *Salmonella typhimurium* susceptible to all third-generation cephalosporins and fluoroquinolones but resistant to penicillins, including amoxicillin/clavulanic acid. Ceftriaxone was substituted for prior antibiotics. The computed tomography (CT) scan of his brain is shown in the figure.

Figure CT scan of brain

Questions

- 1 What is the most likely cause of the CT appearances?
- 2 What bacteria are the most frequent causes of septicaemia in HIV-positive patients?
- 3 How would you explain altered mental status and coma in this patient?

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Answers

QUESTION 1

Diffuse cerebral oedema.

QUESTION 2

Bacterial causes of septicaemia in HIV-positive, non-AIDS patients are, in order of frequency: staphylococci, *Streptococcus pneumoniae*, β -haemolytic streptococci, and non-typhoidal salmonella.¹

In AIDS patients, bacterial causes of septicaemia are, in order of frequency: *Mycobacterium avium-intracellulare*, staphylococci, non-typhoidal salmonella, *Streptococcus pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa*.²

QUESTION 3

Alteration of mental status and coma are found in 23% of cases of septicaemia regardless of the causing bacteria.³ Neurologic alterations are principally due to septic encephalopathy as a consequence of septic emboli, thrombophlebitis, vasculitis or altered brain metabolism and are associated with a poor outcome.³ In rare cases, such as the one presented, they may be a consequence of diffuse septic cerebral oedema.

Treatment of *Salmonella typhimurium* septicaemia should consist of antibiotic treatment with ceftriaxone or fluoroquinolones. In the rare cases of hypersensitivity reaction to β -lactam antibiotics and concomitant resistance to fluoroquinolones, treatment with chloramphenicol or trimethoprim/sulfamethoxazole should be considered. Adequate antibiotic treatment is also the principal therapy of diffuse septic cerebral oedema; additional treatment with dexamethasone, hyperventilation and elevation of the patient's head may be beneficial.

On the sixth day the patient started to react to painful stimuli. By the ninth day his temperature was down to 37.2°C and his mental status had improved significantly (Glasgow coma score=12). The follow-up CT scan obtained on the 15th day was normal. Liver enzyme and creatine kinase levels had become normal, and signs of disseminated intravascular coagulation and swelling of the leg had resolved. The patient was extubated and transferred on the 17th day. Except for *S typhimurium*, no other pathogenic microorganisms were found.

Discussion

The incidence of salmonella infection in the HIV-positive population exceeds the general infection rate by about a factor 100. Furthermore, salmonella is more likely to cause both septicaemia and multiple site and recurrent infections in HIV-positive patients, most of these cases being due to *S enteritidis*.⁴ However, in a recent study, the incidence of *S typhimurium* septicaemia in a HIV-positive group also was increased to 86/100 000/year as compared with 0.575/100 000/year in the general population.⁴

Encephalopathy is considered to be a typical feature of typhoid fever present in about 10% of cases.⁵ However, it is also found in 23% of cases of septicaemia, regardless of the causing

Types of cerebral oedema

- cytotoxic, with blood-brain and CSF-brain barriers intact
- interstitial, with rupture of CSF-brain barrier
- vasogenic, with rupture of blood-brain barrier

bacteria.³ In septicaemia due to non-typhoid salmonella as in our patient, only a few cases have been reported with coma, although a recent study found it in 9.3% of cases.⁶ To our knowledge, the frequency of cerebral oedema in these cases of septic encephalopathy has never been thoroughly studied and, in the literature, we found no other cases occurring during non-typhoid salmonella septicaemia.

Different explanations for the development of septic encephalopathy have been proposed, including multiple septic emboli, endotoxin effects, inadequate cerebral perfusion, immune complex mediated vasculitis and altered brain metabolism,³ though there is no convincing evidence for a key role of any of these factors in pathogenesis. The causes of septic cerebral oedema are even less clear. However, a recent study reported high levels of phospholipase A₂ in patients with typhoid fever,⁷ an enzyme known to catalyze the degradation of phospholipids and to mediate the production of arachidonic acid, a substance which increases capillary permeability.⁸ Thus, there is some evidence that, in typhoid fever, and maybe in septicaemia in general, the cerebral oedema may be of the vasogenic type.

As the pathogenesis of septic cerebral oedema is not quite clear, optimal treatment is unknown. In a case of typhoid fever, a recent article reported a definite decrease of cerebral oedema after treatment with dexamethasone and mannitol,⁹ but in our case a similar decrease was achieved with adequate antibiotic therapy alone. While the benefit of steroids has been established in peritumoral oedema,¹⁰ their role in septic cerebral oedema is less obvious. However, since dexamethasone decreases the capillary permeability induced by phospholipase A₂^{10,11} and arachidonic acid,⁸ there is good reason to believe that it might be beneficial in septic cerebral oedema. Mannitol, however, has been shown to exacerbate vasogenic cerebral oedema after repeated injection by penetrating the injured blood-brain barrier and thus increasing brain osmolality¹²; its use in septic cerebral oedema might therefore be deleterious. However, as in other complications of septicaemia, the key to successful treatment of septic cerebral oedema is adequate antibiotic therapy. Additional treatment with dexamethasone, elevation of the patient's head and hyperventilation may be beneficial.

Final diagnosis

Salmonella typhimurium septicaemia complicated by diffuse cerebral oedema.

Keywords: HIV, septicaemia, *Salmonella typhimurium*, encephalopathy, cerebral oedema

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Abnormal abdominal CT scan following cholecystectomy

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A 65-year-old woman presented with a six-week history of a painful right loin swelling that had failed to resolve despite several courses of oral antibiotics. Ten months earlier she had undergone elective cholecystectomy following recurrent episodes of acute cholecystitis. A laparoscopic approach was attempted but this was converted to an open operation when an empyema of the gallbladder with dense adhesions was encountered. There was no recognised spillage of bile or stones at surgery. Following the operation, she developed a discharge from the wound, which grew *Klebsiella*. This persisted for several months and was managed with a course of oral antibiotics and dressings.

Examination revealed a febrile, unwell woman, with a large tender swelling over the right loin. A computed tomography (CT) scan was performed (figure). The swelling was incised and drained 1.1 litre of purulent material which grew *Escherichia coli* and *Klebsiella*, and two solid fragments which were submitted for biochemical analysis. She received a course of intravenous antibiotics, following which she made a good recovery and was discharged home six days later.

Figure Abdominal CT scan

Questions

- 1 What abnormality does the CT scan show?
- 2 What is the underlying cause of this complication, and what is the nature of the solid fragment?
- 3 What is the significance of the microbiology culture results?

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