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Double Trouble: Decoding The Lethal Co-Infection Of *Clostridium perfringens and Neisseria meningitidis*

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1. Abstract

This case report details a rare co-infection scenario involving two potent pathogens, Clostridium perfringens and Neisseria meningitidis, leading to septic shock in a 65-year-old patient with a fatal outcome. Being diagnosed post-mortem reflects the virulence and rapid course of the disease. To our knowledge, this is the third published case of polymicrobial bloodstream infection with C. perfringens and N. meningitidis. The objective of this study is to deeply investigate the complicated interactions of bacteria in cases of co-infection and draw more attention to considering multiple infections in cases of septic shock. Further in-depth research of these disease interactions and their outcomes could provide vital diagnostic and therapeutic benefits.

2. Keywords: Blood Culture, Sepsis, Co-infection, C. perfringens, N. meningitidis.

3. Introduction

This case report describes the fatal condition of a 65-year-old patient who succumbed to septic shock with the presence of Clostridium perfringens and Neisseria meningitidis in the blood culture. These two organisms are notorious for their ability to cause invasive and severe disease, and this case represents a rare and revealing co-infection scenario.

Clostridium perfringens is a gram-positive anaerobic spore-forming bacillus commonly found in our natural environment as well as in normal human intestinal and vaginal microbiota which can produce several toxins and cause a range of infections, varying in severity from mild to severe [1], such as gas gangrene, enteritis/enterocolitis, and enterotoxaemia [2]. Although rare, bacteraemia is potentially fatal as red blood cell destruction leads to haemolysis and septic shock, which has a very high mortality rate [1].

Neisseria meningitidis is an encapsulated, aerobic gram-negative diplococcus [3]. It is a significant cause of morbidity and mortality in children and young adults worldwide, with epidemic or sporadic meningitis and/or sepsis [3].

This is one of very few documented cases of a patient presenting with bacteraemia due to both C. perfringens and N. meningitidis, resulting in a fatal sepsis. This case study aims to explore the possible factors that could have contributed to the simultaneous occurrence of these two infections in the patient. Additionally, it seeks to identify which of the two germs found in the bacteriological culture is most likely responsible for the severe shock reaction.

4. Case Presentation

A previously healthy 65-year-old female patient was discovered in a state of somnolence by her relatives at her place of residence. Upon arrival at the ICU, the patient's condition was found to be alarming, exhibiting signs of somnolence, unresponsiveness, with normal pupillary reactions. She was hemodynamically unstable, tachypneic, with obvious central cyanosis and peripheral oxygen saturation that could not be accurately assessed. Her body temperature was recorded at 39 degrees Celsius. The patient presented with widespread livid discolouration and petechial haemorrhages. Neither external wounds nor evidence of gas gangrene were observed. No indication for bowel perforation or colon cancer was identified.

A review of her medical history revealed no pre-existing conditions. A history of alcohol consumption cannot be ruled out. Her son reported that she was used to having a glass of wine in the evening. Smoking and illicit drug use were denied by her family members. The subject's most recent appointment with her primary care physician was in 2021. She had been gainfully employed as a gardener and regularly participated in the weekly market. In the two weeks preceding her admission, her general health exhibited a progressive decline. One week prior to the current admission, she has undertaken an 8-hour train journey with her colleagues.

Initial laboratory investigations revealed the presence of severe lactic acidosis and persistent hypoglycaemia. The coagulation parameters were markedly depressed, consistent with the clinically evident bleeding tendency, and accompanied by thrombocytopenia (28,000/µl). The first blood sample showed haemolysis, which was

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initially attributed to a collection error with normal haemoglobin and red blood cells. However, the next results showed an anaemia of 6.9 g/dl, red blood cells: 2.3 10*6/µl, haematocrit: 21.8%, Quick: 52%, fibrinogen: 111 mg/dl, LDH: 1,487 U/l, bilirubin: 1.6 mg/dl which correlated with probable haemolysis and disseminated intravascular coagulation. The patient's white blood cell count was 3,350/µl, creatinine 2.52 mg/dl, AST 509 U/l, ALT 260 U/l, lipase 228 U/l, CRP 13.1 mg/l. The serum lactate concentration was 6 mmol/l and the procalcitonin was 256.3 U/l.
Two pairs of blood cultures were obtained. C. perfringens was identified in the anaerobic culture, while N. meningitidis, serogroup Y, was isolated on two occasions from the aerobic cultures. The urine culture revealed the presence of Escherichia coli at a concentration of >= 10^5/ml, in addition to an undeterminable amount of the Streptococcus salivarius complex.

Computed tomography imaging showed the presence of a localised discrete right pleural effusion, with adjacent lung sections exhibiting evidence of dystelectasis and discrete segmental consolidation in the right lung's lower lobe. This is likely to be a consequence of infiltration. Several uncomplicated parenchymal cysts, reaching a maximum diameter of 2.5 cm, were identified in the liver, accompanied by a subtle prominence of the intrahepatic bile ducts.
The gallbladder and pancreas were poorly demarcated, which may be attributed to an intense inflammatory process. Differential diagnosis included lipomatosis. A mild ascites was observed in the region of the left Gerota's fascia, which may be related to pancreatitis.

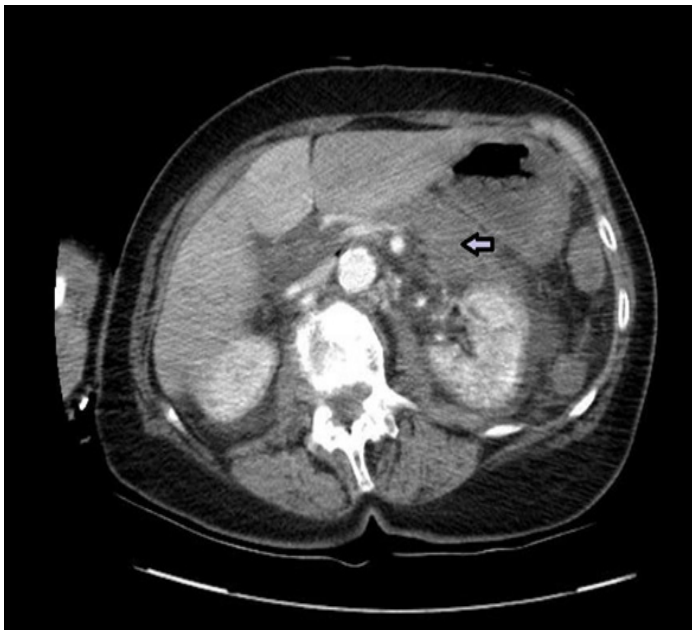

Figure 1: Abdominal computed tomography showing that the gallbladder and pancreas were poorly demarcated, which may be attributed to an intense inflammatory process.

Emergency intubation and treatment with volume replacement and catecholamine administration followed. A clinical bleeding tendency was observed during the procedure of inserting the central venous catheter. The laryngoscopy revealed the presence of a blood clot in the oropharynx.
Subsequently, coagulation factors were substituted (10 g fibrinogen, 6,000 IU Prothrombin complex concentrate (PPSB), 2 units of fresh frozen plasma (FFPs)), and two units of thrombocyte and erythrocyte concentrates were transfused.

Antimicrobial therapy with tazobactam was initiated. However, with the progression of shock symptoms, the therapy was expanded to include vancomycin and meropenem. Despite the implementation of intensive intervention, the patient's condition continued to deteriorate. Ultimately, the patient succumbed to her illness within a span of 24 hours, due to multi-organ failure and a therapy-refractory, fulminant septic shock (SOFA score 16).

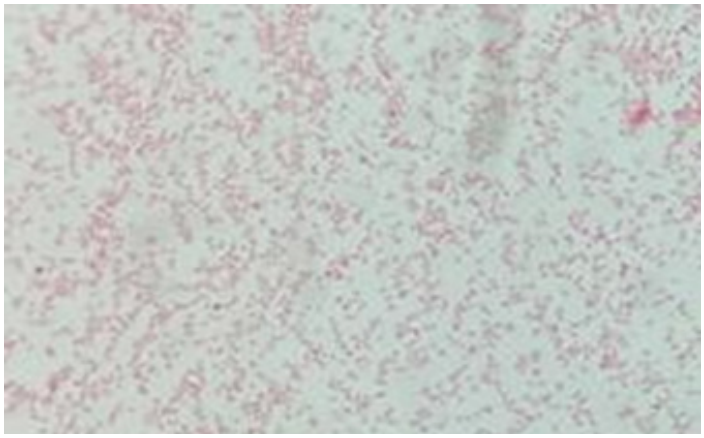

Figure 2: N. meningitidis micrograph. Smear made from blood culture.

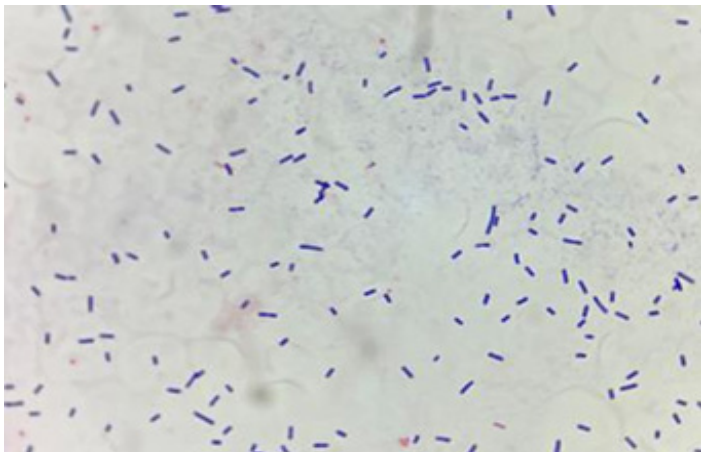

Figure 3: C. perfringens micrograph. Smear made from blood culture.

5. Discussion

Although rare, C. perfringens has the potential to cause one of the most severe forms of bacteraemia, as evidenced by a mortality rate of 27-48% [4]. The production of a multitude of virulent toxins is the primary factor contributing to this high level of lethality [5].
C. perfringens has five recognised serotypes (A, B, C, D and E) and the ability to produce four distinct toxins (α, β, ε and ι) [6]. The α-toxin, predominantly found in type A strains, is considered

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a crucial pathogenic factor in the destruction of soft tissue and the formation of gangrene and gas-forming abscesses. It has the ability to disrupt the membrane of erythrocytes due to phospholipase C activity, which results in haemolysis [6]. It is regrettable that no typing was conducted in this instance, which has resulted in the type and toxins remaining unknown.

Early diagnosis and initiation of appropriate treatment for C. perfringens bacteraemia can be challenging because clinical symptoms are frequently unspecific [7]. Massive intravascular haemolysis can be observed in up to 15% of patients, leading to a mortality rate of 70% to 100% in those cases [8,9].

Regarding our case, the patient succumbed to her illness within a span of 24 hours, due to multi-organ failure and a therapy-refractory, fulminant septic shock (SOFA score 16). According to the blood test, the patient had acute massive intravascular haemolysis and disseminated intravascular coagulation, yet there was no discrepancy in red blood cell (RBC) or haemoglobin (HB) levels. The diagnosis and management of the patient reported here were clearly adequate.

It can be asserted that the combination of haemolysis and infection should prompt consideration of C. perfringens as the potential causative agent, necessitating the rapid administration of an appropriate antibiotic regimen consisting of a combination of a beta-lactam antibiotic and clindamycin or metronidazole [1].

The risk factors for C. perfringens bacteraemia include advanced age and the presence of multiple comorbidities, such as renal insufficiency, haemodialysis, malignancy, heart disease, diabetes, Crohn's disease, COPD, stroke, asthma, as well as colonoscopy and gynaecological procedures [4,7,10]. The most common source of the bacteraemia is intra-abdominal colonization with a relevant association between gastrointestinal or genitourinary malignancies [4]. Other reasons for C. perfringens bacteraemia may also include brain abscess, injuries or inflammation of the urinary tract, pancreas, small bowel, oesophagus, or rarely choledocholithiasis [10], as well as some haematological malignancies [11].

In the case reported here, the patient had no medical history of diabetes mellitus, gastrointestinal diseases or malignancy. Likewise, we had no information on immunosuppressive conditions. Also, no malignant neoplasm was identified on investigations, including the CT abdomen and thorax. It is regrettable that we do not have further information on the patient, since she had not visited the primary care physician since 2021. She was previously employed as a gardener. It is possible that microtraumas may have occurred, with direct inoculation of C. perfringens as a potential cause.

Furthermore, the patient presented with elevated liver function tests accompanied by a subtle prominence of the intrahepatic bile ducts, leading to consideration of biliary source for her bacteraemia despite normal gallbladder seen on the abdominal imaging. However, the CT imaging indicated that the pancreas was poorly demarcated, which may be attributed to an intense inflammatory process that may be related to acute pancreatitis. Given that alcohol consumption could not be completely excluded, it is possible that either alcohol or C. perfringens infection was the cause of the acute pancreatitis.

In a study conducted by Suzaki et al., it was found that in 20–30% of the 60 documented cases of C. perfringens bacteraemia, the main inflammatory lesion of the bacterial entrance was difficult to identify [8].

Several studies have suggested that all identified cases indicate the presence of clinically meaningful bacteraemia, despite the majority lacking identifiable infection sources. Conversely, numerous other studies postulate that instances of Clostridium bacteraemia could frequently represent either contamination, transient bacteraemia, or conditions with negligible to non-existent clinical significance [7,12].

In our case, one positive blood culture for C. perfringens was identified out of two sets, with no clear source directly associated with this kind of infection. Additionally, two blood cultures showed the presence of N. meningitidis. While this combination may suggest contamination with C. perfringens, it is also possible, that C. perfringens bacteraemia created a suitable environment for the proliferation of N. meningitidis.

N. meningitidis has only humans as natural host and can be transmitted from the nasopharynx by aerosol or secretions [13]. 10% to 35% of young adults are estimated to be carriers without symptoms [14].

N. meningitides typing in our patient revealed serogroup Y, which is known to cause meningococcal pneumonia in elderly populations. Additionally, it is responsible for a considerable proportion of meningococcal disease cases, including meningitis and meningococcaemia, among infants under six months of age [3]. There were neither records of vaccination against N. meningitidis in the patient's history, nor was there any evidence of infection in her travel contacts in the following weeks after her death. It is possible that our patient was a chronic carrier of N. meningitidis, or that she was infected during her long train journey a week earlier.

Our patient presented with widespread livid discolouration, petechial haemorrhages with disseminated intravascular coagulation, which could indicate a meningococcaemia with a fulminant progression, and potentially Waterhouse-Friderichsen syndrome (WFS). This syndrome represents a rare complication of sepsis, most frequently occurring in the context of meningococcal infection. It is characterised by a profound adrenal insufficiency, resulting from the acute haemorrhagic necrosis of both adrenal glands [15], which is difficult to diagnose in-vivo and therefore is often defined at autopsy only [16]. The mortality rate associated with WFS is considerable, with estimates ranging from 50% to 95% [15]. However, absence of clinical evidence of meningitis in patients, like ours, presenting with meningococcaemia may lead to missed diagnosis and lack of timely treatment.

Therefore, in our case, the collapse of the immunological defences due to Clostridium perfringens bacteraemia mediated by its toxins may have provided an opportunity for N. meningitidis to enter our patient's bloodstream and cause an invasive form of the disease.

To our knowledge, this is one of very few cases of polymicrobial

bloodstream infection with C. perfringens and N. meningitidis. So far, only two articles have been published on similar co-infections. The first publication from 1984 described a nine-years-old patient with chronic meningococcemia and sepsis associated with bacteraemia due to C. perfringens [17]. The second article was published in 1975 and evaluated 114 cases of C. perfringens bacteraemia. It stated that this phenomenon was often unrelated to the clinical setting and was found in patients with conditions such as alcoholism with aspiration or pneumonia caused by Streptococcus pneumoniae, pulmonary tuberculosis, empyema, meningococcemia, and infantile gastroenteritis [18]. Such unique cases could contribute to a deeper understanding of microbial interaction and immune responses during co-infection, guiding clinicians to consider the possibility of multiple pathogenic invaders in septic shock cases.

6. Conclusion

The simultaneous presence and potential interaction of pathogens such as C. perfringens and N. meningitidis within an individual is an unusual occurrence that poses a significant health threat. This co-infection can result in the exacerbation of inflammatory responses, which may potentially lead to the development of damaging immune reactions and septic shock. While such co-infections are rare, it is crucial to establish the sequence of infection, as one organism may potentially weaken the host's immune system, thereby increasing their vulnerability to the other infection. The early diagnosis achieved through rapid detection methods, in conjunction with the administration of appropriate antibiotic therapy, has the potential to improve patient outcomes.

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