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A CASE OF *RAOULTELLA ORNITHINOLYTICA* CHOLANGITIS IN A LIVER TRANSPLANT RECIPIENT

Daan A. De Coster[1], Melissa Carroll[1], James Lavender[1], Robert Gibson[1,2]

[1] Gastroenterology Department, John Hunter Hospital, Newcastle, Australia
[2] School of Medicine and Public Health, University of Newcastle, Newcastle, Australia

Corresponding author's e-mail: decosterdaan@doctors.org.uk

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ABSTRACT

Background: We present the first documented case of *Raoultella ornithinolytica* bacteraemia in a patient with liver transplantation. *R. ornithinolytica* is a Gram-negative anaerobic bacterium found in aquatic environments in fish and birds, and is source of nosocomial infection causing pneumonia, enteritis, cholangitis or urinary infections, associated with surgical interventions in a hospital setting.

Case description: A 44-year-old female presented with a 2-day history of fever, rigors, and headache. Her past medical history was significant for having received three orthotopic liver transplants due to Wilson's disease over a 20-year period. Her physical examination was unremarkable besides stigmata of prior liver transplantation. Blood tests revealed mild elevations in liver function markers and raised inflammatory markers. *R. ornithinolytica* was eventually isolated from blood cultures. Subsequent magnetic resonance cholangiopancreatography (MRCP) demonstrated new left intrahepatic ductal dilation with heterogeneous peripheral enhancement. The proximal location of the cholangitis explained the lack of abdominal pain or tenderness. The patient was treated with appropriate antibiotic therapy and cultures were negative on day 2. The patient recovered without further intervention.

Conclusion: Seldom encountered *R. ornithinolytica* is uncommonly pathogenic but should be considered in patients receiving immunosuppressants and those with complex surgical anatomy.

KEYWORDS

Liver transplant, transplant complications, cholangitis, rare infections, *Raoultella ornithinolytica*

LEARNING POINTS

- This is the first case of Raoultella cholangitis in a liver transplant recipient described in the literature.
- Atypical clinical presentation and atypical infections are common in this patient group.
- Cholangitis should be suspected in all liver transplant recipients due to immunosuppression.

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INTRODUCTION

We present an unusual case of *Raoultella ornithinolytica* bacteraemia in a patient with liver transplantation. *R. ornithinolytica*, rarely pathogenic in humans, is a Gram-negative anaerobic bacterium found in aquatic environments, in fish or birds and their meat, and is nosocomial in hospitals, causing pneumonia, enteritis, cholangitis or urinary infections[1]. It has been associated with surgical interventions[2], but to date, there are no documented cases of disease in liver transplant patients[1-5].

CASE DESCRIPTION

A 44-year-old woman presented with fever, rigors, diaphoresis, headache and pleuritic left-sided chest pain for 2 days. Her past medical history included 3 orthotopic liver transplants due to Wilson's disease. The first transplant, 20 years ago, failed soon after she received an ABO-incompatible liver, and she was re-transplanted. Her third transplant was 1 year prior to presentation, due to recurrence of fibrosis and chronic rejection, accelerated by pregnancy. After a myositis-type reaction to tacrolimus, her immunosuppressant therapy was changed to mycophenolate mofetil 750 mg twice daily, ciclosporin 50 mg in the morning and 75 mg in the evening, and prednisolone 5 mg daily. She was a non-smoker, did not drink alcohol, and was functionally independent. On history and examination, no focal source for the fever was identified. Her vital signs were an initial temperature of 38.5°C, a respiratory rate of 16 breaths per minute, oxygen saturation of 97% on room air, blood pressure of 104/62 mmHg and a pulse rate of 89 beats per minute. Apart from the initial fever and her borderline hypotension, the patient's vitals were stable for the rest of the admission, and she looked well. Her abdomen was soft and non-tender and there was no clinical jaundice. Initial investigations were unrevealing with negative urine dipstick and a normal electrocardiogram. Her venous lactate was 1.6 mmol/l. The white cell count was 9 $\times 10^9$/l) and the C-reactive protein level was 167 mg/l. Renal function was normal but there was a mildly elevated bilirubin of 50 µmol/l (reference: <20 µmol/l), with a gamma-glutamyl transferase (GGT) of 38 U/l, alkaline phosphatase (ALP) 77 U/l, alanine aminotransferase (ALT) 33 U/l, aspartate aminotransferase (AST) 26 U/l. A chest X-ray demonstrated minimal chronic linear atelectasis in the left base only. Given that the patient presented with pleuritic chest pain and was allergic to radioiodine precluding a computed tomography pulmonary angiogram (CTPA), a ventilation/perfusion (V/Q) scan was performed with no evidence of pulmonary embolism. She was started on appropriate empiric antibiotics to cover underlying immunosuppression with cefazolin (due to a penicillin-related rash), vancomycin and gentamicin at normal doses.

On day 2, blood cultures isolated *R. ornithinolytica* (resistant to: ampicillin/amoxycillin, cefazolin; sensitive to: amoxycillin-clavulanate, ceftriaxone, gentamicin, co-trimoxazole, ciprofloxacin). She developed a morbilliform itchy skin rash on her trunk and limbs that did not improve with antihistamines. She was treated for presumed ascending cholangitis with intravenous ceftriaxone 1 g daily for 3 days followed by oral ciprofloxacin 500 mg twice daily for a total of 14 days on recommendation with microbiology and her managing liver transplant team. Ciprofloxacin was favoured over co-trimoxazole due to mild chronic kidney disease (creatinine 115 µmol/l, estimated glomerular filtration rate [eGFR] 50 ml/min/1.73m^2). The other antimicrobial agents were not favoured due to being either parenteral or beta-lactams. The patient was discharged after 5 days with negative blood cultures. She was followed up in the outpatient setting with improvement in liver function (bilirubin 14 µmol/l), normalisation of her C-reactive protein level, and resolution of the skin rash. Subsequent magnetic resonance cholangiopancreatography (MRCP) demonstrated left intrahepatic ductal dilation with heterogeneous peripheral enhancement. This extended to an 18 mm segment of narrowing *(Fig. 1)*. This stricture of yet indeterminate aetiology was not present on post-transplant imaging 1 year prior and was both too distal to consider intervention and subsequently asymptomatic. Liver function tests in the last year have not shown any more abnormalities and regular follow-up scans (non-contrast CT scans and liver ultrasound scans) have not shown any intrahepatic dilation. A repeat MRCP may be of academic interest.

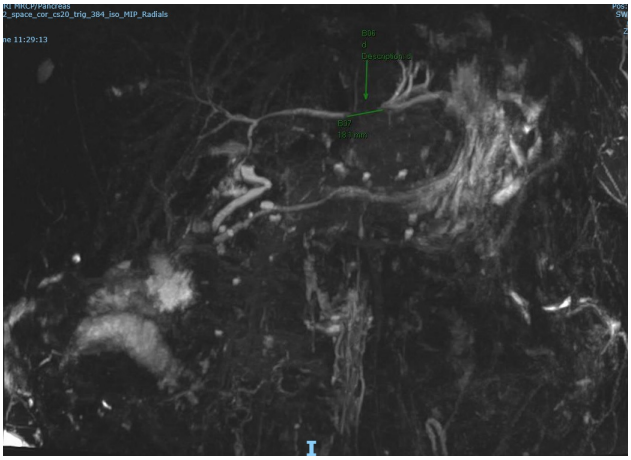


Figure 1. A T2-weighted magnetic resonance cholangiopancreatography (MRCP) coronal slice of the 18 mm biliary stricture in the left intrahepatic biliary duct (top middle, labelled green).

DISCUSSION

Initial assessment did not reveal a clear source for the presentation, thought likely to be contributed to by the patient's underlying immunosuppressed state. However, on day two, *R. ornithinolytica* was isolated from blood samples collected at the time of admission. High inflammatory markers and a raised bilirubin led to dedicated biliary tree imaging to better characterise the transplanted liver. An MRCP revealed a biliary stricture in the left intrahepatic branch of the biliary tree, with peripheral enhancement. As the area of cholangitis was small and proximal, this likely explains why the patient had no right upper quadrant

tenderness. Our patient did not present with classical signs and symptoms of *R. ornithinolytica* infection. Non-nosocomial infection is associated with a scombroid rash. This usually occurs with fish food poisoning (scombroid fish such as mackerel[4]). *R. ornithinolytica* can form a biofilm on contaminated fish, or be present in the fish's gut and convert histidine to histamine through histidine decarboxylase[6,7]. This will manifest with more histamine-release symptoms, such as diarrhoea, vomiting and pruritis[1]. However, scombroid rash rarely lasts more than 14 hours[1], unlike in our patient. It is possible that in this case, her rash was due to vancomycin flushing syndrome, previously known as red man syndrome[8]. However, the rash neither appeared immediately with vancomycin administration, nor disappeared quickly on cessation of the drug. Other drug-related morbilliform rashes classically develop 1-2 weeks after a new exposure, which was not the case here. The patient could however have had this immediate rash because of cross-reactivity between penicillins - she had a documented penicillin-related rash - and the cefazolin given on admission. Cross-reactivity is described as being more likely with first-generation cephalosporins than the third-generation ceftriaxone administered later[9].

To date, there have been no documented/published cases of *R. ornithinolytica* in liver transplant patients. Raoultella species are very similar to Klebsiella species and may have been under-identified in the past, depending on local microbiology identification methods[10,11]. *R. ornithinolytica* has been associated with hepatobiliary disease[1], and most commonly in patients with previous biliary interventions[12]. The propensity for *R. ornithinolytica* to form biofilms[13] make it an important nosocomial agent and it can be associated with high rates of antimicrobial resistance[2]. Due to beta-lactamase, all Raoultella species have intrinsic resistance to amoxicillin, but case series show excellent susceptibility to third-generation cephalosporins, macrolides and quinolones. Occasional studies also report high rates of resistance to amoxycillin-clavulanate[10]. This is similar to our patient's isolate's resistance profile.

Given the paucity of data in the literature, it is unclear whether this rare infection will have a long-term impact on the patient's liver graft health. She responded quickly to antimicrobial treatment which prevented any acute decline in her transplant function. One year later, she continues to be in good clinical condition, with satisfactory biochemical parameters. Repeat magnetic resonance imaging has not yet been undertaken. Her evening mycophenolate dose has been reduced to 500 mg which will decrease her risk of future infections.

CONCLUSION

This case highlights the importance of awareness of rare infections in patients who have undergone solid-organ transplantation. Seldom encountered Raoultella bacterium is uncommonly pathogenic but should be considered in patients on immunosuppressants and with complex anatomy. Prompt recognition and diagnosis is paramount in preserving the transplanted organ and preventing patient deterioration.

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