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Case Report

First reported case series of *Candida krusei* peritonitis secondary to a perforated viscus

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ABSTRACT

Candida peritonitis is associated with high mortality and multiple organ failure. With an evolving epidemiology of candidaemia indicating an increasing prevalence of rare *Candida* species worldwide, consideration of multidrug-resistant fungal pathogens as a cause of abdominal sepsis is paramount. We report three cases of *Candida krusei* as a cause of secondary and tertiary peritonitis. These cases highlight that the early use of an echinocandin class antifungal in patients not responding to standard regimens warrants consideration.

Keywords: Candida peritonitis, *Candida krusei*, Anti fungal, Organ failure

INTRODUCTION

Candida peritonitis has an incidence of 3-12% and is associated with high mortality, prolonged hospital admission and increased health care costs.[1,2] *Candida krusei* is an uncommon *Candida* species worldwide, accounting for 2.5% of candidaemia isolates.[3] It is a potentially multidrug-resistant fungal pathogen due to its intrinsic fluconazole resistance and decreased susceptibility to other antifungals.[4,5] Although an uncommon isolate, *Candida krusei* is an important differential as a cause of abdominal sepsis.

We report three cases of *Candida krusei* peritonitis secondary to perforated viscus. Out of note, all *Candida krusei* isolates were resistant to fluconazole and treated with anidulafungin. These cases demonstrate the need to consider early echinocandin class antifungals administration in patients not improving on standard antifungals.

CASE REPORT

Case 1

A 62-year-old female presented with a 24 hour exacerbation on a background of a 2 week history of right upper quadrant pain. The pain was sharp and severe in nature and occasionally radiated to the right shoulder. It was associated with nausea, but no vomiting, fevers or fatty food intake. Her significant comorbidities included type 2 diabetes mellitus and cirrhosis secondary to non-alcoholic steatohepatitis. On presentation, her vital signs were normal and mild tenderness was elicited in the epigastric and right upper quadrant region.

Serum biochemistry on admission was normal with no elevation in inflammatory markers. After a period of observation with no improvement in her pain, a computed tomography (CT) of the abdomen was performed. It demonstrated extensive pneumoperitoneum and a mural defect involving the anterior part of the duodenal bulb

with mural thickening and surrounding stranding (Figure 1).

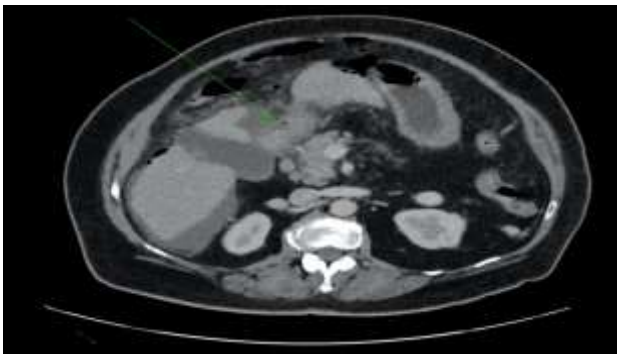

Figure 1: Axial view shows thickening and surrounding stranding of duodenal bulb with pneumoperitoneum.

The patient was initiated on intravenous antibiotic (ceftriaxone and metronidazole) and proton pump inhibitor (PPI) therapy. She underwent diagnostic laparotomy which revealed a perforated duodenal ulcer at the first part of the anterior wall measuring 1x1cm with significant purulent contamination of the peritoneum. As per our normal regime, peritoneal fluid was cultured at operation. The perforation was repaired using a Graham patch and the peritoneal cavity was washed with saline. Postoperatively, she became septic and preliminary isolates of the peritoneal fluid were identified as *Candida krusei*. Intravenous anidulafungin therapy was commenced (200 mg loading dose and then 100 mg daily). Formal sensitivities demonstrated the isolates were fluconazole-resistant and susceptible to anidulafungin.

After appropriate antifungal treatment was commenced, the patient improved clinically with no signs of septic shock at 48 hours. She was discharged on voriconazole 125 mg twice daily for 7 days. At one month follow up visit, the patient was well.

Case 2

An 82-year-old female presented with generalised abdominal pain, nausea and vomiting for 1 day. The patient was disoriented on admission and history was provided by her son. She had no associated fevers, diarrhoea or dysuria. Her last bowel movement was two days ago. Her medical history included type 2 diabetes, hypertension and transient ischaemic attack. On examination, she was disorientated but afebrile and haemodynamically stable. Her abdomen was soft but globally tender with guarding and percussion tenderness.

The arterial blood gas (ABG) demonstrated pH 7.38, pCO2 27, pO2 89, HCO3 16, base excess -7 and lactate 2.0. Laboratory investigations demonstrated a lipase of 475 but were otherwise normal including inflammatory markers. CT abdomen demonstrated multiple pockets of free gas under left hemidiaphragm adjacent to stomach with loculated free fluid within the peritoneal cavity (Figure 2).

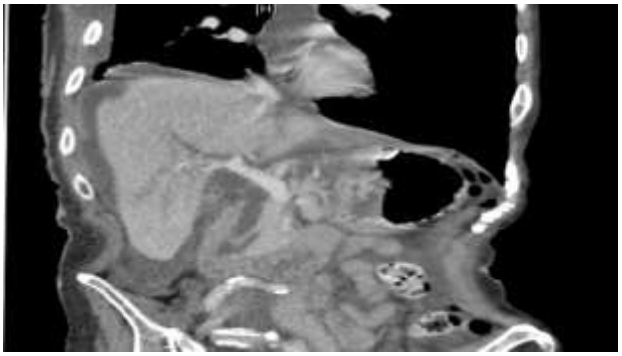

Figure 2: Coronal view shows multiple pockets of free gas under left hemidiaphragm adjacent to stomach.

The patient was initiated on intravenous antibiotic therapy (ceftriaxone and metronidazole) and underwent a diagnostic laparoscopy which demonstrated a 1cm perforated duodenal ulcer with bilious purulent free fluid. Peritoneal fluid was cultured at operation. The procedure was converted to a laparotomy and the perforation was repaired using an omental patch with washout of the peritoneal cavity. Intravenous fluconazole and PPI therapy was commenced. Postoperatively, the patient was admitted to the ICU and required vasopressor and ongoing ventilatory support. Preliminary isolates of the peritoneal fluid identified *Enterobacter cloacae* and yeast. Antimicrobial and antifungal therapy was switched to cefepime, metronidazole and anidulafungin. In 24 hours, the patient demonstrated clinical improvement with improving biochemical markers and was subsequently extubated. Formal isolates of the peritoneal fluid identified *Candida krusei* which was resistant to fluconazole and susceptible to anidulafungin. Secondary to severe angioedema, the patient's antimicrobial therapy was switched to meropenem. She was also commenced on caspofungin to complete her 2 week course of antifungal therapy.

The patient's postoperative recovery was complicated by type 1 respiratory failure likely secondary to hospital acquired pneumonia or aspiration. She deteriorated significantly and was commenced on the end of life pathway with palliative care involvement and passed away 21 days post operatively.

Case 3

A 66-year-old male was admitted for an elective subtotal gastrectomy with gastrojejunostomy for *Helicobacter pylori* chronic gastritis. His medical history included obstructive sleep apnoea, a previous open appendicectomy and cholelithiasis with previous ERCP. He was obese, a heavy smoker (60-pack year history) with a history of heavy alcohol use. 8 hours post operatively, the patient showed signs of septic shock:

heart rate 120 bpm, respiratory rate 34, blood pressure 70/40 mmHg, oxygen saturations 80-85% on 15L O2 via Hudson mask. On examination his abdomen was soft but distended and appropriately tender along laparotomy wound. The patient was admitted to the intensive care unit (ICU).

ABG demonstrated metabolic acidosis with severe lactatemia, pH 7.21, pCO2 36, pO2 56, HCO3 14 and lactate 10.0. Serum biochemistry showed white cell count of 13.0, haemoglobin of 120, creatinine of 338 (baseline 80). Mobile chest X-ray showed bibasal atelectasis but no pneumoperitoneum. CT Pulmonary angiogram and mesenteric angiogram showed no acute pulmonary embolism or active intraabdominal haemorrhage respectively.

The patient was intubated in the intensive care unit due to worsening haemodynamic compromise. He underwent three relook laparotomies. Significant findings included an intraabdominal infected haematoma, retroperitoneal necrotic tissue and a duodenal stump leak. Multiple peritoneal cavity washouts were conducted. A cholecystectomy was performed and Foley's catheter was inserted to manage the duodenal stump leak and facilitate fistula tract development. Final peritoneal cultures demonstrated growth of *Morganella morganii*, *Candida glabrata, Candida krusei and Enterococcus faecalis*. The patient's postoperative recovery was complicated by hospital acquired pneumonia which was treated successfully with appropriate antimicrobial therapy. He received a total of 4 weeks of intravenous therapy of ampicillin, cefepime and anidulafungin.

The patient was discharged on ciprofloxacin 500 mg BD and metronidazole 400 mg TDS for a further two weeks. At one month follow up, the patient was well and the catheter was removed from the duodenostomy.

DISCUSSION

Candida peritonitis occurs in 37-43.4% of patients with upper gastrointestinal perforations.[1,6] In a study of 407 patients with perforation peritonitis, Pramod et al showed a 9% versus 19% mortality rate comparison between non-Candida vs *Candida* peritonitis.[1] Due to its high incidence and mortality rate, the possibility of *Candida* infection should be considered in all patients with upper gastrointestinal perforations. It is especially critical in high risk groups such as immunocompromised patients, individuals with diabetes mellitus, *Candida* colonisation, anastomotic leak and long-term broad-spectrum antibiotic use.[1,7,8] In our case series, two of the three cases had *Candida* peritonitis secondary to duodenal ulcer perforations while the third patient had a duodenal stump leak. In all cases, fungal infections were considered and prophylactic therapy was commenced within 72 hours.

Candida krusei is an uncommon organism, accounting for 3-9.6% of Candida isolates in peritoneal fluid cultures.[9,10] It is more commonly found in individuals with neutropenia, haematologic malignancy, chronic renal disease and previous azole exposure within one month.[11-13] However, our case studies demonstrated that *Candida krusei* can affect immunocompetent patients with minimal comorbidities. Its clinical importance is attributed to its intrinsic resistance to fluconazole due to an altered cytochrome P450 isoenzyme and decreased susceptibility to amphotericin B.[4,5,14,15] In a review of seven randomised trials, Andes et al demonstrated that resistance of the causative *Candida* to the initial antifungal agent may result in delayed treatment and contributed to a higher mortality rate. Similar to our case series, Cascio et al reported a case of *Candida krusei* peritonitis secondary to a duodenal perforation initially treated with fluconazole and replaced with caspofungin.[16,17] This led to resolution of the patient's septic shock within 48 hours. As such, *Candida krusei*, as a causal pathogen for abdominal sepsis should be considered in all patients not responding to standard antifungal therapy.

The 2012 European Society of Clinical Microbiology and Infectious Diseases guidelines recommend fluconazole prophylaxis in candidates with recent abdominal surgery and gastrointestinal perforations or anastomotic leakage.[13] However, the 2016 Infectious Diseases Society of America guidelines suggest echinocandins for initial therapy in patients with clinical evidence of intra-abdominal infection and significant risk factors for candidiasis including recent abdominal surgery, anastomotic leaks or necrotising pancreatitis.[7] In selected patients who are not critically ill and unlikely to have a fluconazole resistant *Candida* species, fluconazole therapy is appropriate.[7] We agree with the recommendations proposed by the Infectious Diseases Society of America and suggest the consideration of multidrug resistant fungal pathogens such as *Candida krusei* as a cause of abdominal sepsis and support the early use of echinocandin antifungal therapies in high risk patient populations. Further research on patient characteristics predisposing multi-drug resistant fungal infection is required. This would allow better risk stratification to determine candidates for initial echinocandin antifungal therapy.

CONCLUSION

Candida krusei is an unusual pathogen associated with peritonitis secondary to perforated viscus. Consideration of multidrug-resistant fungal pathogens as a cause of abdominal sepsis is critical in individuals not responding to standard antifungal therapy. A heightened clinical awareness to the risks of fungal contamination in abdominal sepsis, particularly when dealing with patients who are immunosuppressed is worthwhile including as a component to modern acute care practice.

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