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Biliary co-infection by multidrug-resistant *Candida glabrata* and *Candida albicans* in a case of pancreatic cancer with cholangitis: A case report and review of literature

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ABSTRACT

Herein, we report a case of pancreatic cancer with acute cholangitis secondary to biliary obstruction. Empirical antibiotic therapy did not change the clinical presentation. Blood cultures were sterile; however, bile culture was positive for yeasts. Our laboratory analysis revealed a biliary coinfection by multidrug-resistant C. glabrata and C. albicans. The patient was successfully treated with endoscopic biliary drainage.

1. Introduction

Acute cholangitis due to malignant biliary obstruction is associated with increased mortality among pancreatic cancer patients [1]. Recurrent biliary obstruction, therapeutic hepatobiliary procedures such as endoscopic biliary stents, and percutaneous transhepatic biliary drainage (PTBD) are major factors for cholangitis in patients with pancreatic cancer [2,3]. Although acute cholangitis is commonly considered a primary obstructive phenomenon due to bacteriobilia, biliary candidiasis is an area of ongoing investigation especially in immunocompromised patients with cholangitis [4].

Various factors may predispose patients with hepato-pancreato-biliary malignancies and concomitant cholangitis to biliary candidiasis, including chemotherapy and immunosuppressive agents used in patients with cancer, parenteral hyperalimentation, and long term broad-spectrum antibiotic therapy [4]. Moreover, the growing concerns of drug-resistant candidiasis and the emergence of multidrug-resistant (MDR) *Candida* species pose a serious threat to patient outcomes, especially among immunocompromised individuals [5]. Thus, treatment of biliary candidiasis is problematic, and in many patients, eradication cannot be achieved. *Candida albicans* is the most frequent species isolated from biliary candidiasis followed by *Candida glabrata*, however, co-infection by the organisms has not been described. Herein, we report a case of pancreatic cancer with cholangitis that was co-infected by MDR *C. glabrata* and *C. albicans*.

2. Case presentation

A 49-year-old Persian male patient was diagnosed with pancreatic cancer and liver metastasis with involvement of the superior mesenteric artery (SMA), resulting in unresectable pancreatic cancer (day −120). He received standard induction chemotherapy with dose modifications of cytarabine and idarubicin based on elevated liver enzymes.

After two cycles of chemotherapy (day 0), the patient was found to be febrile and deeply jaundiced with intense abdominal pain and diarrhea. In routine laboratory findings no leukocytosis was observed. The liver function tests showed a markedly elevated alkaline phosphatase (708 U/L) with moderate elevation of direct bilirubin (2.1 mg/dl) and aminotransferases (AST 54 IU/L). In view of obstructive jaundice, fever, and abdominal pain (Charcot's triad) and dilated common biliary duct

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(CBD) on transabdominal ultrasonography, the diagnosis of acute cholangitis secondary to biliary obstruction was made and the patient was empirically started on vancomycin (1 g every 12 hr.) and imipenem (500 mg every 12 hr.) intravenouslyThe patient underwent endoscopic retrograde cholangiopancreatography (ERCP) to drain the infected bile for microbiological examination and palliate obstructive jaundice (day 2). After sphincterotomy and biliary stent placement, complete drainage was established. Bacterial culture of bile was negative and also the blood culture was sterile. However, bile culture was positive for yeast-like fungi. The suspected colonies were subcultured on CHROMagar *Candida* (Paris, France) that resulted in the appearance of two colony phenotypes (Fig. 1).

Two yeast isolates were identified using PCR-sequencing by universal fungal primers (ITS1; 5′- TCCGTAGGTGAACCTGCGG-3′) and (ITS4; 5′-TCCTCCGCTTATTGATATGC-3′) primers.

DNA was extracted from the 12-h fresh colony culture of the two yeast isolates. Then, the ITS regions of the ribosomal DNA gene were amplified by specific primers [6].

For identification, the PCR product was subjected to sequencing (Bioneer, Korea). The obtained sequences were compared with the similar sequences in the open-access NCBI database (http://blast.ncbi.nlm. nih.gov/Blast.cgi). Results of the alignment with BLAST revealed a 98.9 % and 99.1 % identity with *C. albicans* and *C. glabrata*, respectively.

The antifungal drugs containing amphotericin B (AMB; Sigma-Aldrich, St. Louis, MO, USA), caspofungin (CFG, Merck Sharp & Dohme, Haarlem), and fluconazole (FLC; Sigma-Aldrich, St. Louis, MO, USA), were used according to the Clinical and Laboratory Standards Institute M27-S3 standard method and M27-S4 documents by microdulution broth method [7].

The drug dilution ranges tested were 0.016–16 mg/L for AMB, 0.008–8 mg/L for CAS, and 0.063–64 mg/L for FLC. *C. parapsilosis* (ATCC 22019) were used as quality control strains. Antifungal susceptibility testing was performed according the CLSI M27-S3 methodology [7]. The following cut-offs to define resistance were used: MICs ≥2 μg/L for amphotericin B, for caspofungin MIC ≥1 μg/L (*C. albicans)* and MIC ≥0.5 μg/L (*C. glabrata)*, and for fluconazole MIC ≥8 μg/L (*C. albicans*) and MIC ≥64 μg/L (*C. glabrata)* [7]. MICs of the isolates were for amphotericin B 2 and 4 μg/ml; caspofungin 2 and 2 μg/ml; fluconazole 32 and 64 μg/ml for *C. albicans* and *C. glabrata*, respectively. Thus, these findings revealed a biliary infection with MDR *C. albicans* and *C. glabrata*.

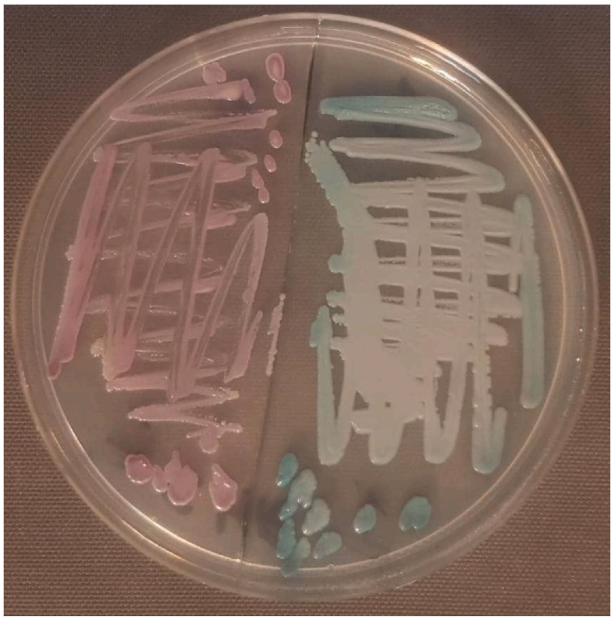

Fig. 1. *Candida glabrata* with pink-colored colonies (left) and *Candida albicans* with green-colored colonies (right) on CHROMagar *Candida*. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Follow-up blood cultures remained negative. When results of cultures and MICs became available, antibiotics were discontinued, but due to the report of *Candida* spp. resistant to available antifungal agents, no antifungal treatment was started. He was discharged (day 7) after ensuring complete biliary drainage, stabilization of vital signs, oral tolerance, and improvement of serum bilirubin and liver tests. The patient was closely observed for five months, with complete clinical and laboratory remission without any evidence of relapse. He is now asymptomatic and has continued his chemotherapy.

3. Discussion

Cholangitis due to bacterial pathogens, particularly gram-negative bacilli, is a common complication in patients with pancreatic cancer who are undergoing biliary drainage procedure. However, fungal infections of the biliary system due to *C. albicans*, *C. glabrata*, *C. tropicalis* have also been reported [4]. Table 1 summarizes reported cases of biliary candidiasis with the patients' demographic characteristics and clinical data.

In light of the diagnosis of acute cholangitis, the initiation of empirical antibiotic therapy was deemed necessary for our patient. Consequently, it is plausible that the negative result of the bile culture for bacteria can be attributed to this therapeutic intervention. Nonetheless, it is noteworthy that the blood culture was collected prior to the commencement of empirical therapy. Because of prior antibiotic administration, the lack of bacterial growth in the bile culture does not entirely exclude bacterial involvement in the etiology of patient's cholangitis. Given the immunocompromised status of the patient, we hypothesized that the fungi may constitute the primary etiological factor. The bile analysis of our case indicated a co-infection of MDR *C. albicans* and *C. glabrata* in a patient with cholangitis as a complication due to pancreatic cancer. This report indicates the challenges encountered in the treatment of obstructing fungal cholangitis by endoscopic biliary stenting. Importantly, endoscopic biliary stenting could also be a major risk factor in the development of future stent-associated cholangitis in our case due to his malignant biliary obstruction; however, several other mechanisms can contribute to cholangitis secondary to biliary obstruction in patients with malignancies. The risk factors for cholangitis include immunosuppression due to chemotherapy or corticosteroid therapy, malignant hematologic disease, broad-spectrum antibacterial administration, diabetes mellitus, improper sterilization of endoscopes or prostheses, previous surgery, or trauma [2,8,9]. Our case exhibited a number of these risk factors, including immunocompromise secondary to systemic chemotherapy for pancreatic cancer and corticosteroid therapy, as well as broad-spectrum antimicrobial therapy.

Unfortunately, the available treatment options for the management of obstructing fungal masses are very limited, particularly for drug-resistant *Candida* strains [5]. So far, to the best of our knowledge, only a few cases of obstructing biliary candidiasis and acute fungal cholangitis have been reported across the world. Some studies support systemic and intrabiliary administration of azole antifungal therapy [5]. Although systemic administration of amphotericin B has been shown to have numerous complications (e.g., nephrotoxicity, fever, rigors, and hypotension), some reports have suggested that local intrabiliary administration could be effective [10]. However, in this case, drainage of the common bile duct was only performed for fungal eradication. Of note, no antifungal therapy was given, as the isolated *Candida* strains were MDR and there was no evidence of systemic candidiasis. Previously, some authors reported that no further antifungal administration was necessary following bile duct drainage for complete fungal eradication [3,11]. Hence, treating by direct drainage may be a more effective treatment strategy because obstructive fungal masses are easily

Table 1
A summary of reported biliary candidiasis cases.

Study	Year	Country	Underlying condition and predisposing factors	Clinical presentation	Culture result	Treatment	Fungal eradication
Marcucci et al. [3]	1978	USA	cholecystectomy	- Abdominal pain - Jaundice	C. albicans	- Surgical removal of fungal balls & drainage. - No antifungal therapy	Yes
Magnussen et al. [13]	1979	USA	- Acute myelogenous leukemia - cholecystectomy - Chemotherapy - Neutropenia - Broad-spectrum antibiotic therapy	- Fever - Persisted abdominal tenderness - Elevated liver function tests	C. albicans	- Surgical removal of fungal balls - Antifungal therapy with amphotericin B	Yes
Carstensen et al. [14]	1986	Denmark	- blunt abdominal trauma	- Abdominal pain - Jaundice and hepatomegaly	C. albicans	- Treatment with T-tube drainage - Antifungal drugs	Yes
Irani et al. [15]	1986	Iran	- descending thoracic aortic aneurysm	- Abdominal pain - Jaundice and hepatomegaly	C. albicans	- Antifungal therapy with amphotericin B	No (died of cerebral Infarct)
Ho et al. [10]	1988	USA	- Sickle-cell disease - cholecystectomy - multiple blood transfusions - Broad-spectrum antibiotic therapy	- Jaundice and abdominal pain - Postprandial nausea and vomiting - Dark-colored urine	C. albicans and Candida tropicalis	- Treatment with T-tube drainage - Intrabiliary amphotericin B	Yes
Wig et al. [11]	1998	India	None	- Jaundice and abdominal pain - Fever - Intense pruritus - Elevated liver function tests	C. albicans	- Treatment with T-tube drainage - No antifungal therapy	Yes
Reeves et al. [16]	2000	USA	- Gastric carcinoma - total gastrectomy with Roux-en-Y esophagojejunostomy - cholecystectomy	- Weight loss - Abdominal pain - Jaundice - Pruritus - Elevated liver function tests	C. albicans	- Intravenous amphotericin B therapy - Fluconazole administration through jejunostomy tube - Intraluminal amphotericin B treatment - Endoscopic debridement	Yes
Domagk et al. [17]	2001	Germany	- High-degree arteriosclerosis - aortofemoral bypass surgery prolonged antibiotic therapy	- Elevated liver function tests - Extrahepatic bile duct dilation	C. albicans and C. glabrata	- Sphincterotomy - Intravenous fluconazole and flucytosine therapy - Intravenous and intrabiliary liposomal Amphotericin B	Yes
Ballal et al. [4]	2013	India	- Cholangiocarcinoma - Biliary obstruction - prolonged antibiotic therapy	- Fever - Jaundice	C. tropicalis	- Biliary drainage	No

removed from the biliary tract by endoscopic maneuvers.

Our in vitro investigations revealed the isolated candida species to exhibit resistance against all currently accessible antifungal medications within our nation's pharmaceutical market and we lacked readily available sensitive medications for such multidrug-resistant species. However, the patient showed positive response to bile drainage and improvement in clinical status. Furthermore, the limited existing medications, in addition to being expensive and associated with numerous potential side effects, demonstrated resistance in in vitro analyses. Consequently, following consultations with two expert infectious disease specialists, a collective decision was made to discontinue the administration of antifungal agents. However, it is imperative to acknowledge the potential disparity between in vitro and in vivo results in this context [12].

In conclusion, surgical biliary drainage for fungal cholangitis without antifungal treatment showed to be an effective treatment to clear the fungal infection in our patient. In the context of MDR fungal pathogens causing cholangitis, surgical biliary drainage can be considered as the treatment of choice.

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Authors' contributions

Conceptualization: Amir Sadeghi and Mohsen Rajabnia; **Data curation:** Hamidreza Houri and Ensieh Lotfali; **Formal analysis:** Mohsen Rajabnia; **Methodology:** Amir Sadeghi; **Project administration:** Mohsen Rajabnia; **Resources:** Amir Sadeghi; **Software:** Erfan Ghadirzadeh; **Supervision:** Amir Sadeghi and Mohsen Rajabnia; **Validation:** Hamidreza Houri and Ensieh Lotfali; **Visualization:** Erfan Ghadirzadeh; **Writing–original draft:** Erfan Ghadirzadeh, Hamidreza Houri, and Mohsen Rajabnia; **Writing–review & editing:** All authors.

Ethical form

Written informed consent was obtained from the patient or legal guardian(s) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Declaration of competing interest

There are none.

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