

Clinical significance of isolated biliary candidiasis in patients with unresectable cholangiocarcinoma

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BACKGROUND: The frequency of isolated biliary candidiasis is increasing in cancer patients. The clinical significance of isolated biliary candidiasis remains unclear. We analyzed the risk factors of biliary candidiasis and outcomes of the patients with unresectable cholangiocarcinoma after percutaneous transhepatic biliary drainage (PTBD).

METHODS: Among 430 patients who underwent PTBD between January 2012 and March 2015, 121 patients had unresectable cholangiocarcinoma. Bile and blood samples were collected for consecutive fungal culture.

RESULTS: The study cohort included 49 women and 72 men with a median age of 71 years. Multivariate analysis showed that cancer progression ($P=0.013$), concurrent presence of another microorganism ($P=0.010$), and previous long-term (>7 days) antibiotic use ($P=0.011$) were potential risk factors of biliary candidiasis. Chemotherapy was not associated with overall biliary candidiasis ($P=0.196$), but was significantly related to repeated biliary candidiasis ($P=0.011$). Patients with isolated biliary candidiasis showed remarkably reduced survival compared with those without [median overall sur-

vival (OS): 32 vs 62 days, $P=0.011$]. Subgroup analysis was also performed. Patients with repeated candidiasis had markedly decreased survival compared with those with transient candidiasis (median OS: 30 vs 49 days, $P=0.046$). Biliary candidiasis was identified as a poor prognostic factor by univariate and multivariate analyses ($P=0.033$). Four cases of repeated candidiasis (4/19, 21%) showed *Candida* species in consecutive blood culture until the end of the study, but others showed no candidemia.

CONCLUSIONS: Isolated biliary candidiasis may be associated with poor prognosis in patients with unresectable cholangiocarcinoma. Especially, repeated biliary candidiasis may have the possibility of progression to candidemia. We suggest that biliary dilatation treatment or antifungal agents might be helpful for patients with biliary candidiasis.

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KEY WORDS: biliary candidiasis;
biliary obstruction;
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Introduction

Malignant biliary obstruction is a common complication in patients with biliary tract cancer and a potential risk factor for poor outcomes.^[1] Since malignant biliary obstruction may cause cholangitis or sepsis, oncologists should consider this situation as an oncologic emergency.^[2] Currently, many clinicians perform interventional procedures, such as endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic biliary drainage (PTBD), to restore adequate bile duct drainage. Moreover, active treatment with antimicrobial agents, based on bile culture and antimicrobial susceptibility data, often improves clinical outcomes.^[3] Although it is debated whether

PTBD is superior to other procedures for the decompression of bile duct obstruction,^[4] PTBD is useful when endoscopic procedures are not possible, especially in patients with hilar obstruction or surgically altered anatomy.^[5] Additionally, since bile samples from PTBD are less prone to contamination by intestinal microorganisms than those obtained from ERCP, the results of bile culture using PTBD samples are more reliable for decision-making regarding the selection of antimicrobial agents.^[6]

The prevalence of fungal infection of the biliary tract, such as infection due to *Candida* species, is increasing and significant in immunocompromised patients.^[7] *Candida* infection is frequently noted in cases of high-grade biliary strictures or tumor stenosis.^[8] The term “biliary candidiasis” refers to a condition in which *Candida* species are detected in the bile; this condition is an unrecognized clinical problem, particularly in isolated biliary candidiasis, in which *Candida* species are detected only in the bile but not in the blood. Although the reported mortality rate for candidemia is very high,^[9] the association between isolated biliary candidiasis and survival rates is not well known. The present study aimed to analyze clinical risk factors of initially isolated biliary candidiasis. We also investigated the association between isolated biliary candidiasis and clinical outcomes among primary unresectable cholangiocarcinoma patients with biliary obstruction.

Methods

Patients

We reviewed the medical records of 430 patients who had undergone PTBD at our center between January 2012 and March 2015 and identified 296 patients with malignant biliary obstruction and 134 with non-malignant disease. Of the 296 patients with malignant biliary obstruction, 132 had biliary tract cancer and 122 had blood and bile culture at least twice. *Candida* species were isolated from both blood and bile in one case at the beginning of the enrollment which indicated candidemia. This case was excluded from further analysis. A total of 121 patients were analyzed in the present study. Fig. 1 shows the schematic flow of the patient enrollment.

Microbiological analysis and antibiotic therapy

All bile and blood samples were obtained immediately after PTBD. The follow-up culture of bile and blood was performed every 7±2 days after initial culture. Aliquots of all bile and blood samples were placed in sterile tubes and delivered to the microbiology laboratory within 2 hours. The samples were cultured using an automated culture system (BACTEC FX; Becton Dickinson, East

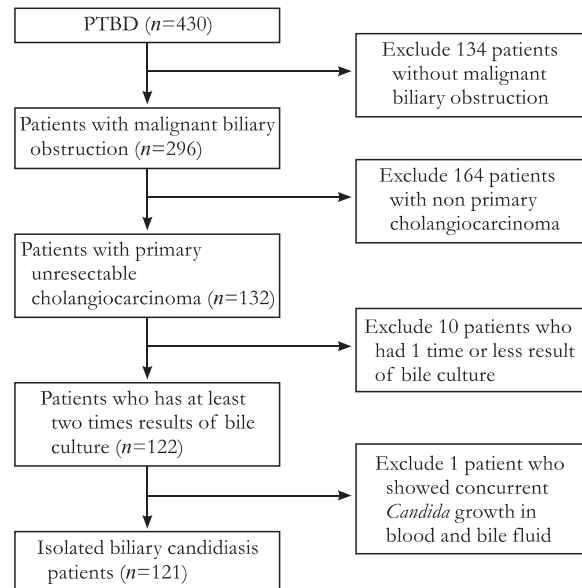


Fig. 1. Schematic representation of the study design. PTBD: percutaneous transhepatic biliary drainage.

Rutherford, NJ, USA). Bacterial identification was performed using the VITEK2 automated system (bioMérieux, Hazelwood, MO, USA). The cultures were incubated for 48 hours, with the first reading at 24 hours. Biliary candidiasis cases were divided into two groups: transient or repeated. Transient candidiasis cases were defined as those with one bile culture positive for *Candida* species, followed by consecutive negative bile cultures until the end of the study. Repeated candidiasis cases were defined as those with two or more bile culture positives for *Candida* species during the study period. Antibiotic treatment was given when the patient had fever (body temperature >38 °C), leukocytosis (>12×10⁹/L), or C-reactive protein levels >1 mg/dL, or signs of systemic inflammatory response or shock (blood pressure <90/50 mmHg) were observed. Since there are no guidelines for the treatment of isolated biliary candidiasis, antifungal treatment was based on the patients’ symptoms and clinicians’ judgment.

Statistical analysis

Continuous variables were expressed as mean and standard deviation. Categorical variables were presented as the total and percentage. The Chi-square or Fisher’s exact test was used to compare categorical variables, whereas Student’s *t* test was used to compare continuous variables. Laboratory parameters were analyzed using the Wilcoxon-Mann-Whitney test. Logistic regression was used for univariate and multivariate analysis of possible risk factors for isolated biliary candidiasis. The effect of antifungal agent on survival and negative conversion of *Candida* species was analyzed by logistic regression. Post-PTBD overall survival (pOS) was calculated from the

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