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Rare common bile duct metastasis of breast cancer: A case report and literature review

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Abstract

BACKGROUND

Breast cancer is the most common tumor in women, and about one-third of cases develop metastatic disease. However, metastatic breast cancer rarely invades the common bile duct (CBD) directly without involving the liver, and involvement of the gastrointestinal tract is rare. Cases of such metastases pose a particular diagnostic challenge.

CASE SUMMARY

A 55-year-old female presented to the Department of Gastroenterology with complaint of a 2 mo history of right upper abdominal pain accompanied by pain in the right back, aggravated after eating greasy diet. The patient had received a diagnosis of breast cancer 3 years prior. Physical examination showed obvious superficial protuberant erythema on the left neck and chest skin, with slight tenderness and burning sensation. Endoscopic retrograde cholangiopancreatography showed an obstruction at the end of the CBD. Histopathology of the CBD and symptomatic skin biopsies showed positivity for cytokeratin 7 and trans-acting T-cell-specific transcription factor breast cancer biomarkers. A cancer embolus was also found in the skin vasculature. Accordingly, the diagnosis of breast cancer metastases to the skin and biliary ducts was made. A plastic biliary sent was placed, which relieved the right upper abdominal pain and protected against unnecessary hepatectomy surgery.

CONCLUSION

Although rare, biliary metastasis should be considered in patients with bile duct stenosis and a history of breast cancer.

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Core Tip: Breast cancer is the most common tumor in women, and about one-third of cases develop metastatic disease. However, metastatic breast cancer rarely invades the common bile duct (CBD) directly without involving the liver, and involvement of the gastrointestinal tract is rare. We report a case of CBD metastasis from breast cancer that was diagnosed according to findings from endoscopic retrograde cholangiopancreatography imaging and histopathology of CBD and symptomatic skin biopsies. This case highlights the importance of making an accurate diagnosis before undertaking an operative approach. Although CBD metastasis of breast cancer is rare, it should not be completely ignored.

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INTRODUCTION

Breast cancer is the most common tumor in women^[1] and about one-third of cases will progress to metastatic disease^[2], which is the leading cause of cancer-related death^[3]. Only 5%-10% of newly diagnosed breast cancer patients present with distant metastasis; more troubling, the risk of developing metastatic disease is high among patients with localized primary disease following successful primary tumor resection and adjuvant therapy^[4-6]. It is estimated that up to 30% of node-negative breast cancer patients will develop metastatic disease, despite receiving standard treatment^[4-6].

Breast cancer metastasis includes contiguous, lymphatic, and hematogenous forms of spread^[7]. While hematogenous spread of breast cancer can target any site in the human body, the most common sites are bone, lung, lymph nodes, liver, and brain^[7]. Metastasis to the digestive system, kidney, and retroperitoneal organs is rare, and to the biliary system is remarkably rare^[8-10]. Widespread liver metastases can compress or infiltrate the bile duct, which may lead to obstructive jaundice, while a direct metastatic involvement of the extrahepatic bile duct in the absence of hepatic lesions is exceptional^[8-10].

We describe, herein, a special case of secondary tumor of the common bile duct (CBD) from a primary breast cancer tumor that had been treated by operation 3 years earlier. Our review of the literature highlighted that this diagnosis may be difficult and controversial in rare sites. For early diagnosis, endoscopy and detailed pathological analysis are necessary, which may help prevent unnecessary surgical intervention.

CASE PRESENTATION

Chief complaints

A 55-year-old female presented to the Department of Gastroenterology (Shanghai East Hospital, Shanghai, China) with complaint of right upper abdominal pain lasting over a 2 mo period that was accompanied by pain in the right back and aggravated after eating greasy diet.

History of present illness

The patient's symptoms started 2 mo prior, with recurrent episodes of right upper abdominal pain.

History of past illness

The patient had been diagnosed with breast cancer 3 years prior but had an

unremarkable medical history otherwise.

Physical examination

Physical examination revealed mild tenderness in the right upper quadrant of the abdomen. Superficial protuberant erythema with clear margins were observed on the left neck and chest; the patient indicated a burning sensation and slight tenderness associated with the erythema.

Laboratory examinations

Laboratory tests upon admission showed elevated gamma-glutamyl transpeptidase (238 IU/L; normal range: 10-60 IU/L) but normal level of alkaline phosphatase (67 IU/L) and negative findings for inflammatory biomarkers. All blood tumor markers (alpha-fetoprotein: 2.01 ng/mL; carcinoembryonic antigen: 1.71 ng/mL; cancer antigen-125: 12.1 U/mL; cancer antigen-199: 9.26 U/mL; and cancer antigen-135: 14.3 U/mL) were within normal ranges.

Imaging examinations

Magnetic resonance cholangiopancreatography revealed enlarged head of the pancreas, narrowed CBD within the pancreas head, and slightly dilated upper bile ducts (Figure 1). Ultrasound gastroscopy revealed changes indicative of chronic pancreatitis, widening of the bile duct wall, and immunoglobulin G (IgG)4-related cholangitis (Figure 2). Subsequent laboratory tests, however, showed the IgG-4 level to be within the normal range, excluding the possibility of IgG4-related cholangitis.

Abdominal enhanced magnetic resonance imaging showed that the wall of the CBD was thickened and became obviously enhanced with contrast agent. The coronal view showed dilation of the upper segment of the CBD, with rough tissue wall and narrowing of the lower segment. Nodular thickening was also seen (localized) in the lower segment of the CBD (Figure 3). Endoscopic retrograde cholangiopancreatography (ERCP) showed an obstruction at the end of the CBD. Biopsies were taken from the affected tissues (CBD end and symptomatic skin lesions; Figure 4). Bone scan showed metastases in the left third rib and the eighth vertebral body (Figure 5).

Further diagnostic work-up

Histopathology results for the biopsied CBD and skin of left neck and chest were: Cytokeratin 7 (+); trans-acting T-cell-specific transcription factor (+); estrogen receptor (ER) (-); progesterone receptor (PR) (-); and human epidermal growth factor receptor-2 (HER2) (-). Morphological characteristics were assessed, and a cancer embolus was found in the skin vasculature (Figure 6).

FINAL DIAGNOSIS

Metastases of breast cancer to the skin and biliary ducts.

TREATMENT

After undergoing ERCP placement of a plastic stent for systemic chemotherapy, the patient was referred to an oncologist who ordered a treatment course of gemcitabine (1000 mg, administered on day 1 and day 8) and cisplatin (30 mg, administered on day 1 to day 3).

OUTCOME AND FOLLOW-UP

The patient eventually died of multiple organ failure caused by severe infection after systemic chemotherapy.

DISCUSSION

Invasive breast carcinoma of no special type is the most common histological type of breast cancer, accounting for 75%-80% of all invasive breast cancer cases.

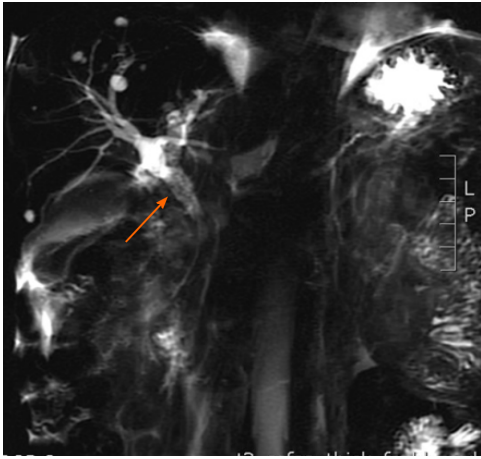


Figure 1 Magnetic resonance cholangiopancreatography. Findings of dilatation of the common bile duct, stenosis of the distal common bile duct, and density shadow of soft tissue are indicated by an arrow.

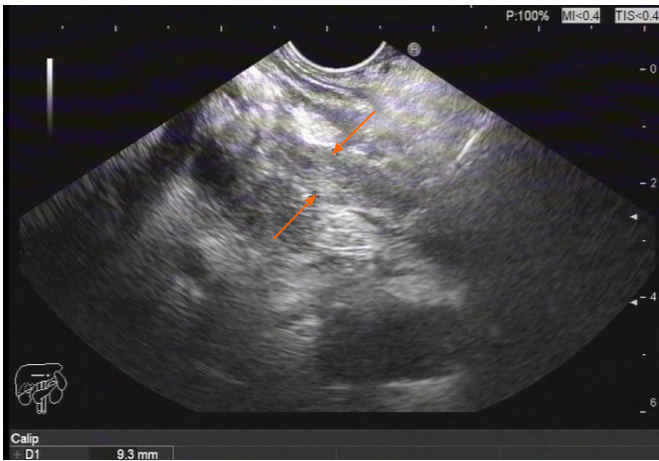


Figure 2 Endoscopy findings. Ultrasound gastroscopy revealed widening of the bile duct wall (arrows).

Gastrointestinal tract involvement is rare, accounting for only about 10% of all cases, but usually occurs in invasive lobular carcinoma^[11]. Through literature review, we found reports of 30 cases of metastatic breast cancer involving the bile ducts, including 7 cases involving CBD^[11-16], 20 cases involving extrahepatic duct^[9,17-21] or lymph nodes extending directly into bile ducts^[12,22] and ampulla of Vater, and 3 cases classified as uncertain^[23] (Table 1). In these cases, the time interval between the diagnosis of breast cancer and the secondary tumor was as long as 21 years and as short as 2 years. Preoperative diagnosis was achieved in only 4 cases, and the others were treated surgically. Rego *et al*^[15] reported on 2 patients with abnormal ampulla and distal CBD stenosis detected by ERCP, with a diagnosis of breast metastasis confirmed by immunohistochemistry before surgical treatment. Budimir *et al*^[11] reported on another case in which ERCP detected CBD stenosis, after which brush aspiration was performed for subsequent cytological analysis. Finally, Cochrane *et al*^[16] reported on a case in which endoscopic ultrasound revealed a mass in the mid-portion of the CBD, with fine-needle aspiration biopsy demonstrating metastatic breast cancer.

Patients with metastatic breast cancer involving the bile ducts may experience abdominal discomfort, upper gastrointestinal bleeding, jaundice and related symptoms, such as pruritus or alterations in stool and urine^[24]; these nonspecific clinical symptoms, being similar to the presentation of primary tumors, complicate the diagnostic process. Moreover, in most cases, there is a long interval between the diagnosis of the primary tumor and the development of metastatic tumors affecting biliary tract function, which poses a further challenge to suspicion of a relationship between the historical breast cancer event and the presenting biliary disease^[13,15,25,26]. Endoscopic diagnosis may be difficult, due to implantation of the metastatic cells in the submucosa. Coletta *et al*^[21] reported that breast cancer metastasis could target the

Table 1 Reported cases of bile duct metastasis of breast cancer

Ref.	Cases, n	Location of secondary tumor	Therapy	Time interval between diagnosis of primary tumor and metastasis
Popp <i>et al</i> ^[12] , 1979	1	CBD	Surgical bypass plus chemotherapy	Average 40 mo
Titus <i>et al</i> ^[13] , 1997	1	Distal bile duct	Pancreaticoduodenectomy	Undetermined
Stoeckler <i>et al</i> ^[14] , 2007	1	Distal bile duct	Pancreaticoduodenectomy	Undetermined
Rego <i>et al</i> ^[15] , 2009	2	Ampulla of Vater and CBD	Surgery and palliative chemotherapy	2 yr
Cochrane <i>et al</i> ^[16] , 2015	1	CBD	Aplastic stent placed, chemotherapy and endocrine therapy	21 yr
Budimir <i>et al</i> ^[11] , 2015	1	CBD	Metal stent implantation and aromatase inhibitors	6 yr
Popp <i>et al</i> ^[12] , 1979	6	Extrahepatic lymph nodes	Radical and palliative surgery, transhepatic drainage, radiation, chemotherapy	Average 40 mo
Kopelson <i>et al</i> ^[17] , 1980	6	Extrahepatic duct	Radical and palliative surgery, radiation, chemotherapy	Undetermined
Engel <i>et al</i> ^[22] , 1980	2	Extrahepatic duct, lymph nodes	Biliary tract resection and choledochojejunostomy	Undetermined
Franco <i>et al</i> ^[9] , 1987	2	Proximal bile duct, bifurcation	Bile duct resection, double choledochojejunostomy	6 and 8 yr respectively
Pappo <i>et al</i> ^[18] , 1991	1	Extrahepatic, intra and extraluminal	Bile duct resection, choledochojejunostomy, cholecystectomy	2 yr
Feliu Villaró <i>et al</i> ^[19] , 1995	1	Extrahepatic intraluminal	Undetermined	Undetermined
Papo <i>et al</i> ^[20] , 1996	1	Extrahepatic intraluminal	Biliary tract resection and choledochojejunostomy	Undetermined
Coletta <i>et al</i> ^[21] , 2014	1	Extrahepatic bile ducts	Cholecystectomy, extrahepatic biliary resection, and double hepaticojejunostomy	13 yr
Rabin <i>et al</i> ^[23] , 1979	3	Undetermined	Undetermined	Undetermined

CBD: Common bile duct.

extrahepatic bile duct without involvement of the lumen or duct mucosa. ERCP sensitivity ranges from 25% to 50% for masses near the hepatic hilum, and negative finding for biopsied tissues is estimated to occur in > 30% of cases^[24]. Thus, the combination of ultrasound-guided biopsy and immunohistochemical analysis plays a key role in the diagnosis of this rare type of secondary tumor.

Early identification and surgical resection of cholangiocarcinoma have been shown to improve the 5-year overall survival^[2]. In the case of primary malignant bile duct tumors, clinicians are likely to recommend surgery, but for patients with metastatic breast cancer, surgery is generally not considered clinically beneficial^[27]. Treatments for metastatic breast cancer are guided by multiple factors, most importantly the expression status of ER, PR and HER2, treatment history, and prognostic indicators (*i.e.* short disease-free interval, presence of visceral metastases, performance status, and degree of symptoms)^[28]. For example, patients with hormone receptor-positive status are expected to benefit from hormone therapy, whereas those with HER2-positive disease are treated with targeted agents (trastuzumab and lapatinib) in conjunction with chemotherapy. In contrast, treatments of patients with triple-negative breast cancer only depend on cytotoxic chemotherapy^[28].

Discordant ER, PR, or HER2 expression status between primary tumors and metastases has been reported^[29]. In addition, the conversion to negative receptor status is, on average, higher than that of positive conversion (24% *vs* 14% for ER; 46% *vs* 15% for PR; 13% *vs* 5% for HER2)^[30]. Two explanations have been put forth for this observation. The first involves technical issues that result in poor reproducibility of immunohistochemistry techniques. The second involves tumor heterogeneity (*i.e.*

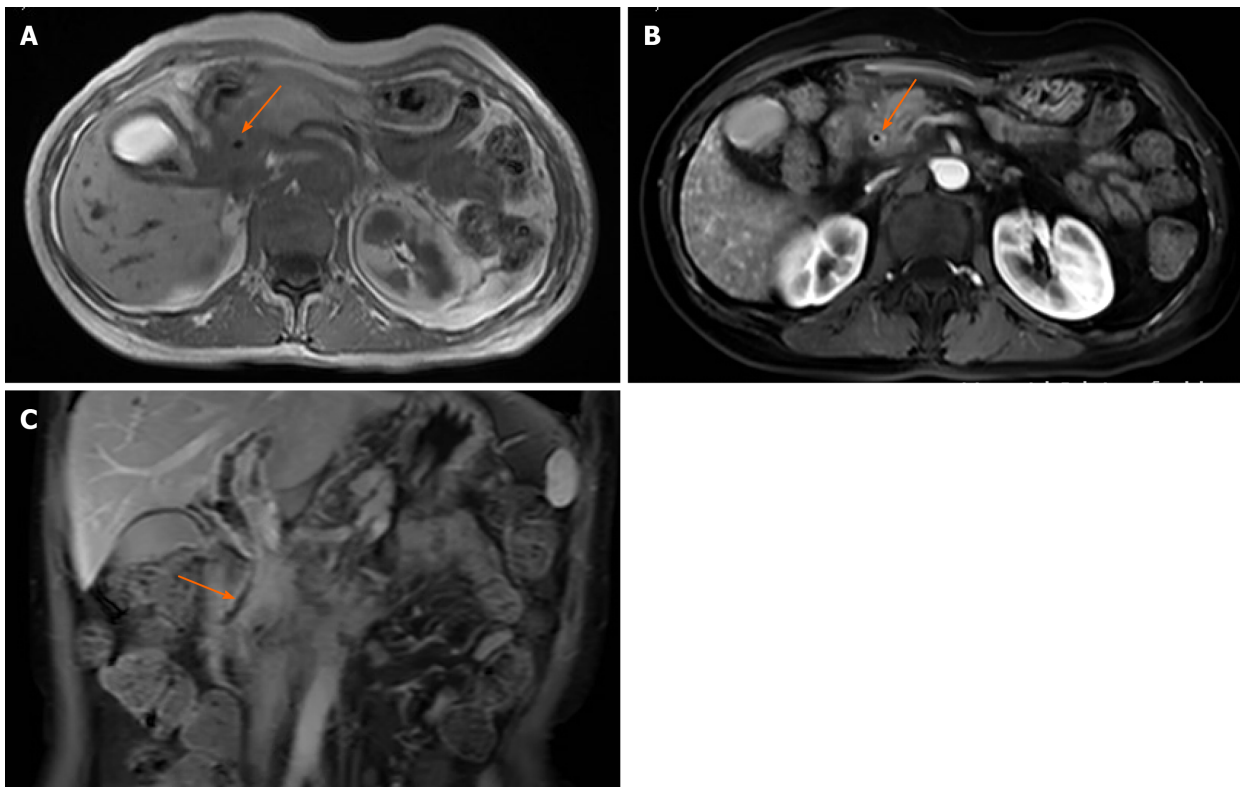


Figure 3 Magnetic resonance imaging of the abdomen. A and B: The wall of the common bile duct was thickened (arrows) and became obviously enhanced with contrast agent; C: Local nodular thickening was seen in the lower segment of the common bile duct (arrow).

subpopulations of cells within the primary tumor and its metastases, having distinct genotypes and phenotypes and possibly different biological behaviors^[31]. Receptor status of breast cancer may indicate both the prognosis and risk of recurrence; for example, ER-positive tumors display protracted metastasis latency periods and frequently metastasize to the bone^[32-35]. In our case, CBD metastasis of breast cancer occurred 3 years after surgical treatment, with multiple bone metastases in addition. Expression of the nuclear protein Ki-67 has been shown to correlate with the proliferative rate of tumor cells and this biomarker is used clinically as an independent prognostic biomarker in primary breast cancer, especially among patients with ER (+) tumors^[36,37]. Therefore, a biopsy of suspected breast cancer metastases would be necessary to determine the appropriate management of the disease.

In general, patients with pancreaticobiliary malignancies, metastatic disease and external biliary compression by lymph nodes should be implanted with plastic or self-expanding metal stents to both relieve related jaundice and abdominal pain symptoms and to improve the overall prognosis^[11]. Surgical bypass or biliary stenting is reported to extend survival to over 1 year, in comparison to un-intervened cases of liver metastases, for whom mean survival is only about 1 mo^[11]. Although many previous reports have indicated the superiority of a metal stent for malignant distal biliary obstruction^[38], we generally prefer to use plastic stents to relieve symptoms before pathological diagnosis is obtained. Thus, only after our patient underwent ERCP placement of a plastic stent was she referred to the oncology department for systemic chemotherapy.

CONCLUSION

In conclusion, we report a special breast cancer case of direct metastasis to the CBD. Although this situation is rare, the possibility of biliary metastasis should be considered in the differential diagnosis of the bile duct stenosis for patients with a history of breast cancer, to avoid unnecessary hepatectomy. The differential diagnosis of cholangiocarcinoma is very important, with advanced endoscopic techniques and pathological diagnosis playing an important role in such.

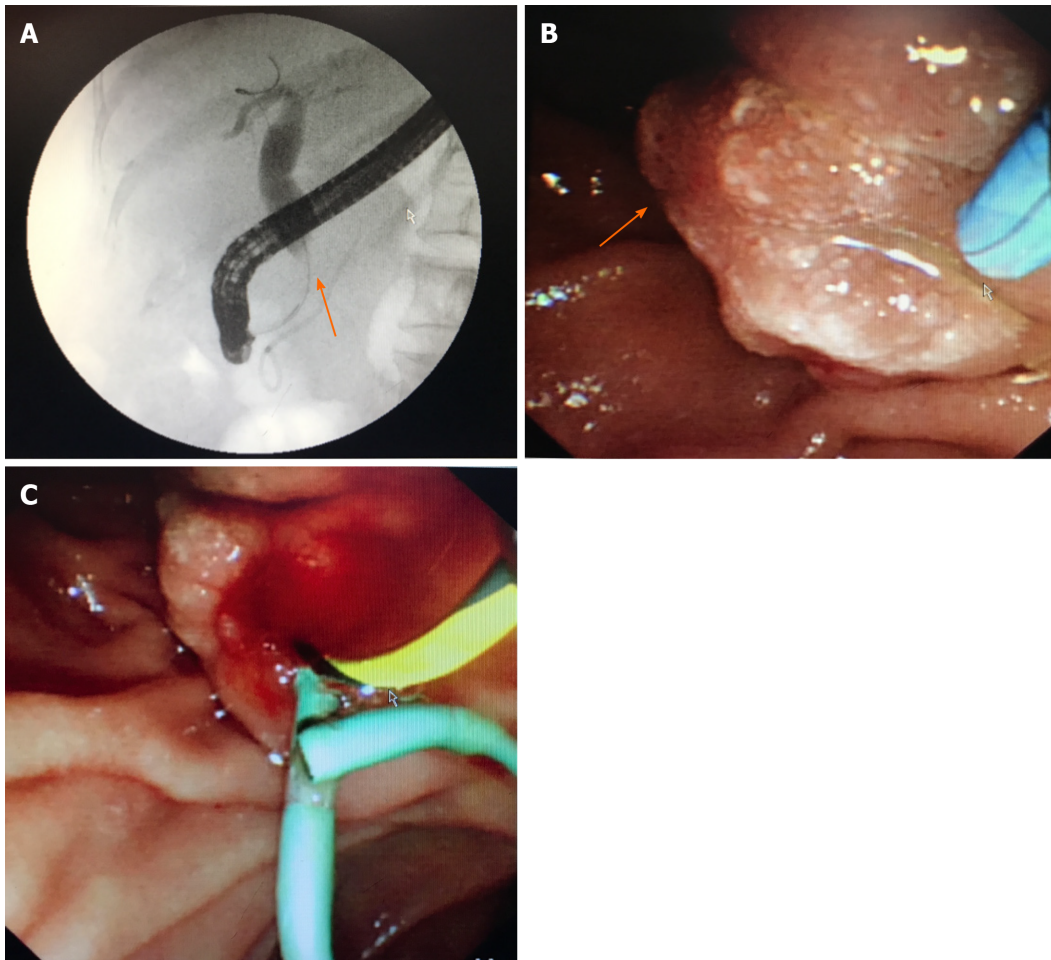


Figure 4 Endoscopy findings. A: Endoscopic retrograde cholangiopancreatography showed dilatation of the common bile duct and stenosis of the distal common bile duct (arrow); B: Edema of the ampulla; C: Implanted plastic stent.

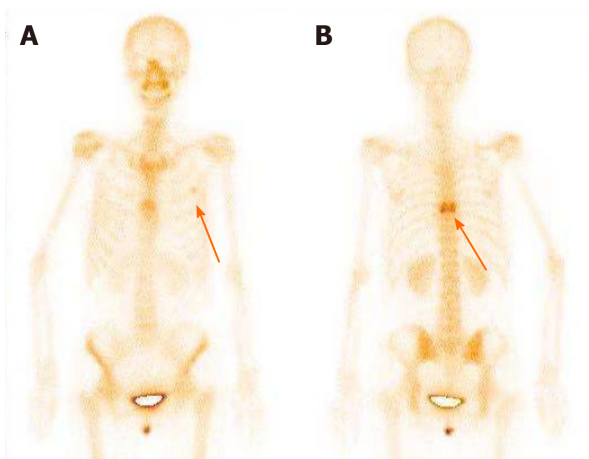


Figure 5 Bone scan findings. A: Metastasized tumors in the left third rib; B: Metastasized tumors in the eighth vertebral body.

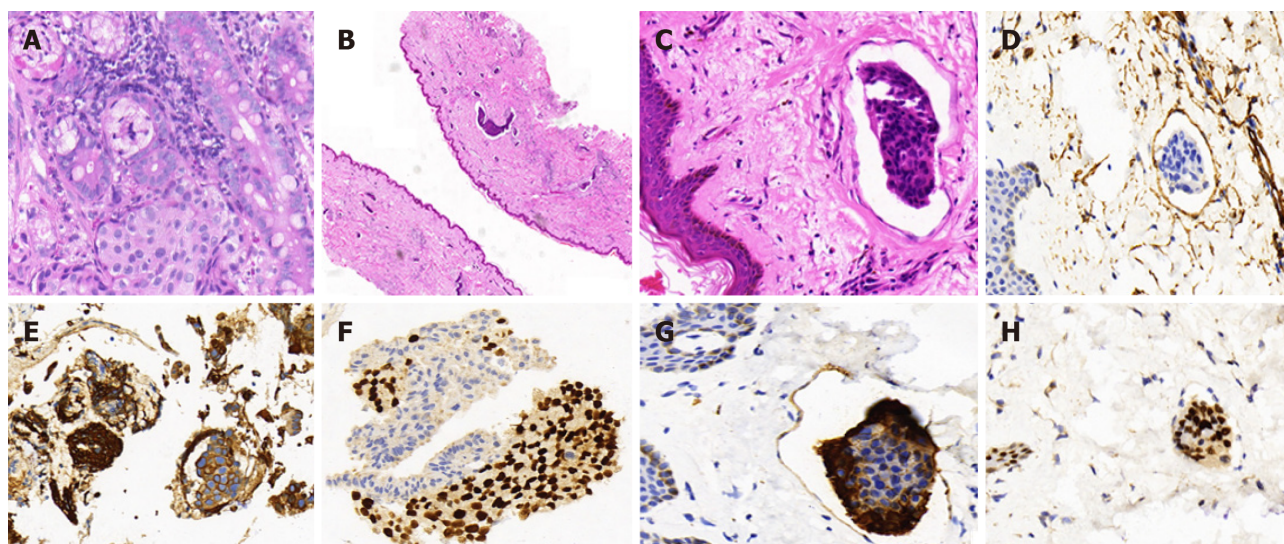


Figure 6 Histopathology of biopsies of the common bile duct and the skin of left neck and chest. A: Cancer cells were found to have infiltrated the glandular duct of the common bile duct (CBD); B and C: Low-power magnifications (B: 2 \times , C: 40 \times) demonstrating cancer embolus in the vasculature of the skin; D: Positive immunohistochemistry (IHC) staining for CD34 in the cancer embolus areas; E and F: Strong positive IHC staining for cytokeratin (CK) 7 and trans-acting T-cell-specific transcription factor (GATA-3) in the CBD; G: Strong positive IHC staining for CK7 in the skin of left neck and chest; H: Strong positive IHC staining for GATA3 in the skin of left neck and chest.

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