

**Ampullary tumor with a rare etiology: A new lesion in the residual ampulla following curative resection of the perihilar cholangiocarcinoma**

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**Authors' contributions:** HT, YM, and AK designed the study. HT and YM drafted the manuscript. YM analyzed the histological slides of surgically resected specimens, and performed tumor sequencing and data interpretation. HT and AK coordinated clinical care and specimen procurement and analysis. AK supervised the study, revised the manuscript for important intellectual content. All authors approved the final manuscript.

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**Question:** A 59-year-old woman was referred to our hospital for jaundice and a liver tumor. Contrast-enhanced computed tomography (CT) revealed an enhanced 25 mm diameter tumor located in segment 5 (S5) near the liver hilum, and the right hepatic artery was involved (**Figure A**). Hilar biliary obstruction bismuth type IIIa was detected by magnetic resonance cholangiopancreatography (MRCP) (**Figure B**). Following endoscopic retrograde cholangiopancreatography (ERCP), intraductal ultrasound (IDUS) revealed hilar biliary obstruction from the proximal common bile duct to the left hepatic duct, and the root of B4 bile duct was intact (**Figure C**). Endoscopic sphincterotomy (ES) was performed for easy access to the tumor (**Figure D**). Using biopsy forceps, tumor specimens were collected from the obstructed left hepatic duct, which tested positive for adenocarcinoma, whereas the root of B4 and distal common bile duct were negative for cancer cells. Therefore, the patient underwent left hepatectomy.

Pathological evaluation revealed perihilar cholangiocarcinoma without dysplasia in the normal-appearing distal bile duct and resection margins. Neither lymph nodes nor liver metastasis was evident; thus, it was classified as T3N0M0 Stage IIIA according to the 8th edition of the TNM staging system.

One year after the curative resection of the perihilar cholangiocarcinoma, a new nodule was detected on contrast-enhanced CT in the residual distal bile duct (**Figure E**). The major duodenal papilla revealed irregular swelling, redness, and erosion (**Figure F**). Endoscopic ultrasonography (EUS) revealed a mass 15 mm in diameter that involved the distal bile duct and invaded the pancreas (**Figure G**).

What is the diagnosis and etiology?

## Answer: Periapillary implantation recurrence of perihilar cholangiocarcinoma after curative left hepatectomy

Pancreatoduodenectomy was performed, and it was observed that the tubular adenocarcinoma occupied the periapillary region. Multi-region genomic mutation analysis was conducted to reveal the potent mechanisms of early periapillary recurrence after curative resection of the perihilar cholangiocarcinoma<sup>1</sup>.

The primary perihilar cholangiocarcinoma had two histologically different compartments that were analyzed separately, namely moderately differentiated adenocarcinoma in the left hepatic duct and poorly differentiated invasive area in the liver S5 (**Figure H**). These components shared *KRAS* G12S, *TP53* G245S, *CDKN2A* D74N, and *PBRM1* T1363QfsTer17 mutations (**Figure I**). The biopsy specimen from the left hepatic duct during the preoperative ERCP possessed the same profile as the moderately differentiated compartment. No mutation was found in the gallbladder, distal bile duct, or resection margins.

The secondary periapillary tumor was also analyzed as a well-differentiated adenocarcinoma adjacent to the distal bile duct. The more prominent components of the moderately differentiated compartment with rich desmoplasia were independently subjected to the sequencing analysis (**Figure J**). Both compartments had a mutation profile similar to that of the biopsy specimens from the left hepatic duct. The well-differentiated compartment was marked by an additional *ARID1A* R429Q, and the moderately differentiated compartment was marked with *ARID1A* H1624Y. None of the mutations were found in the remnant distal bile duct, including the margin of the primary resection.

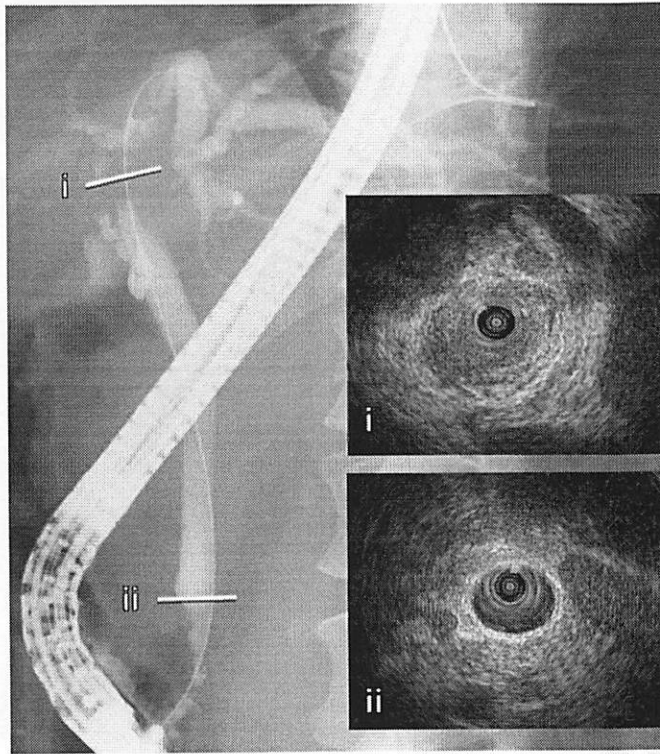
We speculated that the perihilar cholangiocarcinoma might have been implanted in the periapillary region, where the tight epithelium barrier against the bile juice became fragile due to the ES. Another potential factor causing the implantation may be the mechanical seeding of the tumor cells through the biopsy forceps and IDUS. It should be noted that the normal-appearing distal bile duct, surrounding soft tissue, and lymph nodes had no mutations; therefore, the possibility of a continuous spread along the biliary tract and lymphatic metastasis would be modest. Early recurrence in the current case suggests the possibility that endoscopic procedures may alter the seeding potential of the cholangiocarcinoma, albeit infrequently. This is the first report suggesting an apillary implantation recurrence of perihilar cholangiocarcinoma after curative left hepatectomy with precise genomic tracing<sup>2,3</sup>.

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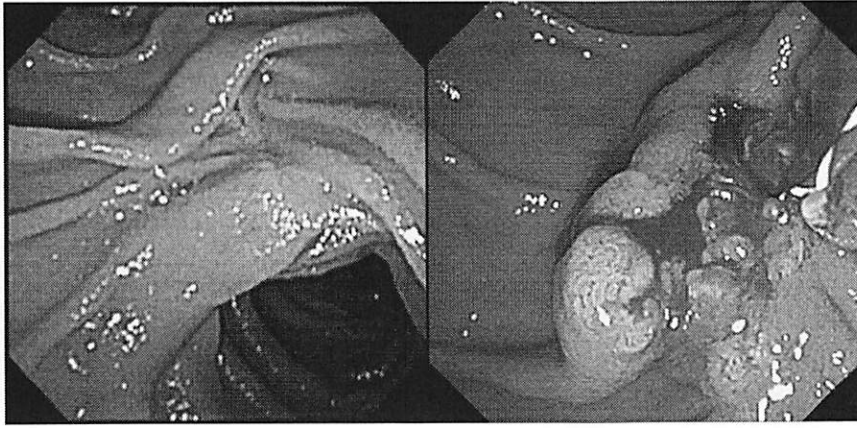
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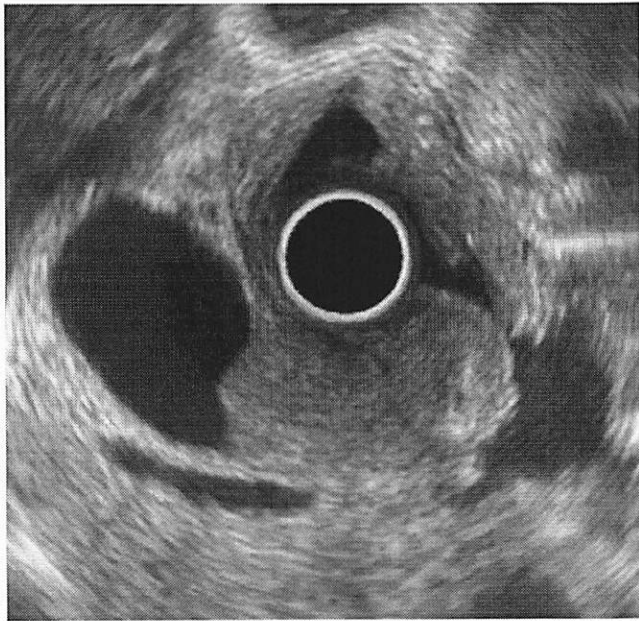


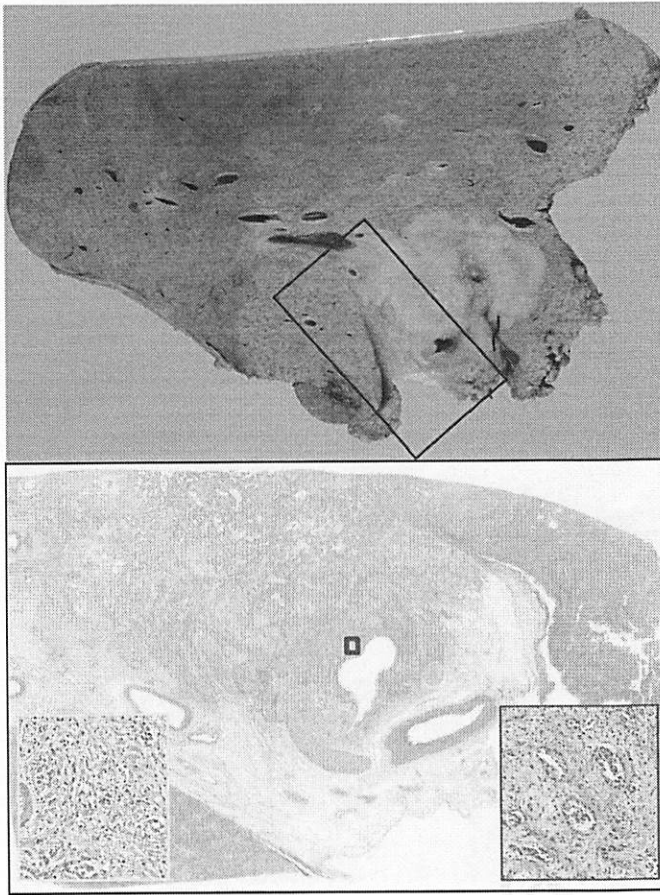


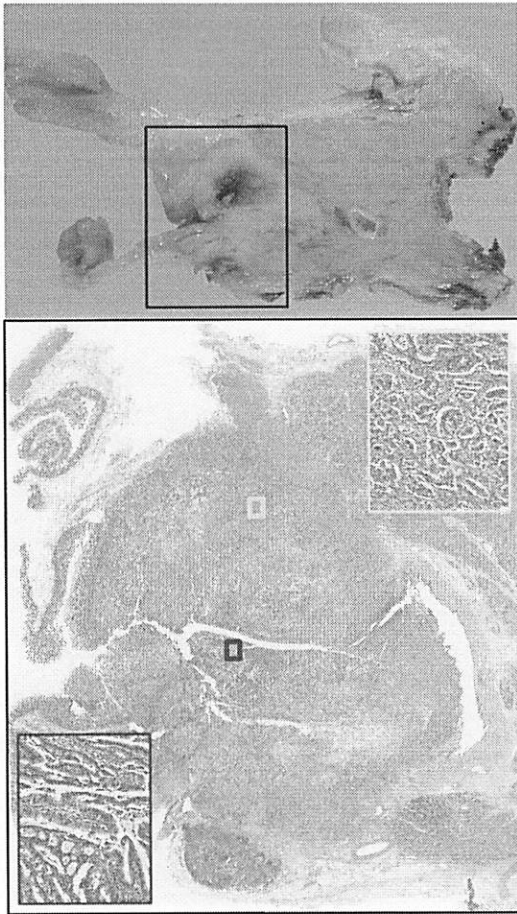


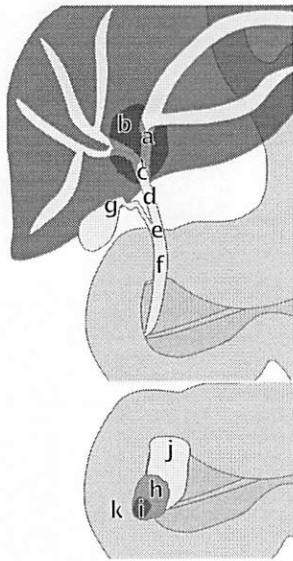












Region	Histology	<i>KRAS</i>	<i>TP53</i>	<i>CDKN2A</i>	<i>PBRM1</i>	<i>KMT2D</i>	<i>NF1</i>	<i>GNAS</i>	<i>ARID1A</i>
a	Perihilar tumor (Left hepatic duct)	moderately differentiated adenocarcinoma	G12S	G245S	D74N	T1363QfsTer17	R5214H	L216M	5'-UTR
b	Perihilar tumor (invaded S5 of liver)	poorly differentiated adenocarcinoma	G12S	G245S	D74N	T1363QfsTer17	R2734Ter		
c	Biopsy specimen from left bile duct	moderately differentiated adenocarcinoma	G12S	G245S	D74N	T1363QfsTer17	R5214H	L216M	5'-UTR
d	Superior bile duct	Normal							
e	Middle bile duct	Normal							
f	Inferior bile duct margin	Normal							
g	Gall bladder	Normal							
h	Ampullary tumor (well)	well differentiated adenocarcinoma	G12S	G245S	D74N	T1363QfsTer17	R5214H	L216M	5'-UTR R429Q
i	Ampullary tumor (moderately)	moderately differentiated adenocarcinoma	G12S	G245S	D74N	T1363QfsTer17	R5214H	L216M	5'-UTR H1624Y
j	Inferior bile duct margin	Normal							
k	duodenum	Normal							