Intrahepatic cholangiocarcinoma initially diagnosed as adenocarcinoma of unknown primary with hepatoduodenal ligament lymph node metastases: A case report

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Abstract. Intrahepatic cholangiocarcinoma (iCCA) with regional lymph node metastases, which lacks a well-delineated liver mass, may be misdiagnosed as a carcinoma of unknown primary (CUP) origin. The present study reports the case of a 69-year-old man initially diagnosed with CUP, who was incidentally found to have abdominal lymphadenopathy during ultrasonography (US). The clinical course from the time of lymphadenectomy and CUP diagnosis to iCCA detection after long-term follow-up is reported. A patient with a history of hypertensive renal disease presented with an incidental finding of enlarged abdominal lymph nodes in the perihepatic region on US. Abdominal contrast-enhanced computed tomography (CT) scan and magnetic resonance imaging (MRI) revealed two enlarged lymph nodes in the hepatoduodenal ligament. Exploratory laparotomy and lymphadenectomy were performed for diagnostic and therapeutic purposes, respectively. Poorly differentiated metastatic adenocarcinoma positive for cytokeratin 7 and negative for cytokeratin 20 was identified in two of the 22 lymph nodes. Postoperatively, a positron emission tomography/CT (PET/CT) scan was performed, which failed to locate the primary site. The diagnosis of CUP was confirmed based on clinical, radiological and histopathological characteristics. A sequential abdominal CT scan 48 months after lymphadenectomy revealed a faintly enhancing, intraductal polypoid mass with localized ductal dilatation in liver segment 3. MRI and PET/CT confirmed a mass in the left lobe of the liver. US-guided percutaneous needle biopsy confirmed the presence of moderately differentiated adenocarcinoma. The patient refused surgical treatment because of general weakness caused by Coronavirus disease 2019 infection. The patient received radical radiotherapy and underwent left hepatectomy after recovery of their performance status. Histopathological examination of the surgical specimen demonstrated prevailing fibrosis and mucin accumulation, with scattered cancer cells observed focally in the resected liver specimen owing to the effect of the radiotherapy. Consequently, a definitive diagnosis of primary adenocarcinoma of the intrahepatic bile duct was confirmed. The present report may improve understanding of the pathophysiology and clinical progression of iCCA, with a specific focus on the intraductal growth subtype.

Introduction

Intrahepatic cholangiocarcinoma (iCCA) is an adenocarcinoma arising from cholangiocytes in bile ducts proximal to second-order branches within the liver parenchyma, with poor outcomes owing to its generally aggressive nature, late-stage diagnosis and lack of treatment options for advanced disease (1,2). iCCA can be hidden and misclassified as carcinoma of unknown primary (CUP) due to difficulty in distinguishing it pathologically from metastatic adenocarcinoma arising from extrahepatic primary tumors. This is especially the case for tumors originating in the foregut, such as the pancreas, esophagus and stomach due to the lack of iCCA-specific immunohistochemical biomarkers (3,4). Numerous cancers previously classified as adenocarcinomas of unknown primary may be iCCA (5). Novel diagnostic modalities, such as CT, MRI imaging and immunohistochemistry, have improved clinical distinction between iCCA and CUP (6). These factors may have contributed to the increasing incidence of iCCA worldwide over the past three decades.

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iCCA is the second most common primary liver cancer after hepatocellular carcinoma, accounting for 10-15% of cases of primary liver cancer (5,7). However, the diagnosis of iCCA remains challenging, and a multidisciplinary approach may be required. CUP is only considered if localized lymph node metastases are detected (8). To the best of our knowledge, iCCA, which initially presents as CUP with localized lymph node metastases, has rarely been reported (9). The present study reports a patient diagnosed with iCCA as CUP and the clinical course from the time of radical lymphadenectomy in the hepatoduodenal ligament and diagnosis of CUP to the detection of iCCA after long-term surveillance.

Case report

A 69-year-old male patient with a history of hypertension presented with an incidentally discovered lymph node measuring 2.7 cm within the hepatoduodenal ligament, suggesting a pathological lymph node, upon serial abdominal ultrasonography (US; Fig. 1A) evaluation due to chronic kidney disease at Veterans Health Service Medical Center (Seoul, Korea) in September 2018. Tumor marker tests were performed; cancer antigen 19-9 (CA 19-9) was elevated to 1,199 U/ml (normal range, 0.0-37.0 U/ml), whereas carcinoembryonic antigen (CEA, 3.6 ng/ml; normal range, 0.0-5.0 ng/ml), prostate-specific antigen (PSA, 2.8 mg/ml; normal range, 0.0-4.0 mg/ml), α-fetoprotein (AFP, 4.2 ng/ml; normal range, 0.0-7.0 ng/ml) and β-human chorionic gonadotropin (0.2 mIU/ml; normal range, <1.0 mIU/ml) were within normal ranges. Abdominal contrast-enhanced computed tomography (CT; Fig. 1B) and magnetic resonance imaging (MRI; Fig. 1C) revealed enlarged hepatoduodenal ligament lymph nodes ~2.7 and 1.5 cm in diameter, respectively, with no detectable liver mass. In October 2018, the patient underwent an exploratory laparotomy and lymphadenectomy for diagnostic and therapeutic purposes, respectively. Intraoperatively, no liver mass was identified, except for enlarged lymph nodes visible to the naked eye. The cut surfaces of the excised pathological lymph nodes had a pale yellow and granular appearance (Fig. 1E). Four-micrometer thick sections were obtained from the formalin-fixed and paraffin-embedded (FFPE) tissue block and stained with hematoxylin and eosin. Under the light microscope, histological evaluation was performed. Histopathological examination revealed poorly differentiated metastatic adenocarcinoma in two of the 22 lymph nodes (Fig. 1F). Immunohistochemical staining for cytokeratin (CK) 7, CK20, thyroid transcription factor-1 (TTF-1), CDX-2, p53, alpha-methylacyl-CoA racemase (AMACR), prostate specific antigen (PSA), and S100 protein were performed on the 4-micrometer FFPE tissue block of the fresh specimen. The slides were stained on the Ventana BenchMark XT platform (Ventana Medical Systems, Tucson, AZ) and on a Leica Bond Max instrument (Leica Biosystems, Chicago, IL) according to the standard protocol (Table I). All slides were evaluated under the light microscope. Immunohistochemistry (IHC) results showed cytokeratin (CK) 7(+; Fig. 1G), CK20 (-; Fig. 1H), thyroid transcription factor 1 (TTF-1) (-), CDX-2 (-), periodic acid-Schiff (PAS) (+), diastase-PAS (-), p53 (+), SMAD-3 (+), α-methylacyl-CoA racemase (-), PSA (-) and S100 protein (-; data not shown). These results suggested a potential origin from the upper gastrointestinal tract and pancreaticobiliary system. Postoperatively, positron emission tomography/CT (PET/CT) was performed; however, the primary site, particularly a hepatopancreatobiliary origin, could not be identified (Fig. 1D). A diagnosis of poorly differentiated CUP was confirmed based on clinical, radiological and histopathological characteristics following tumor board discussion. Following an in-depth discussion with the patient, regular investigations of the tumor marker CA 19-9 and follow-up CT scans were performed without further anticancer therapy, considering patient age and underlying chronic kidney disease. One month after the lymphadenectomy, the CA 19-9 levels decreased to 154.04 U/ml and returned to normal range after 3 months (Fig. 2). During surveillance every 6 months, the CA 19-9 levels remained within the normal range. In October 2022, a CT scan displayed a faintly enhancing intraductal polypoid mass ~1.1 cm in diameter with localized ductal dilatation in liver segment 3 (Fig. 3A), which was also confirmed in the same area on MRI (Fig. 3B) and PET/CT (Fig. 3C). US-guided percutaneous needle biopsy was performed for pathological diagnosis and moderately differentiated adenocarcinoma was confirmed (Fig. 3D). The patient refused a second surgical treatment because of general weakness caused by Coronavirus disease 2019 infection. As an alternative treatment, stereotactic body radiation therapy (60 Gy in four fractions) was initiated, which showed a partial response (Fig. 4A). Gradually, performance status improved and the patient consented to surgical treatment and underwent a left lobectomy of the liver in February 2023. The resected liver specimen revealed a cavitary mass and periductal fibrosis with multifocal hemorrhage (Fig. 4B). Histopathological examination of the surgical specimen demonstrated that fibrosis and mucin accumulation were prevalent and scattered cancer cells were found focally in the resected liver specimen because of the effect of radiotherapy (Fig. 4C) and were too small for further assessment of immunohistochemical markers. Based on these clinical, radiological and histopathological findings, the patient was diagnosed with iCCA, which was accompanied by regional lymph node metastases. As of October 2023, the patient is still alive and undergoing regular surveillance every 3 months without any evidence of local recurrence or metastasis following hepatectomy.

Discussion

The present patient was initially diagnosed with CUP with hepatoduodenal ligament lymph node metastases. During 48-month follow-up after radical lymphadenectomy, a delineated intrahepatic mass was discovered and iCCA was confirmed histopathologically following hepatectomy. The present case report presents a latent diagnosis of iCCA with a clear pathology, initially diagnosed as CUP, and a long-term clinical course without additional anticancer therapy.

iCCA initially diagnosed as CUP has been diagnosed by autopsy: Oda *et al* (9) reported a 57-year-old male with systemic lymph node metastases. Imaging revealed no primary cancer. Autopsy indicated occult intrahepatic cholangiocarcinoma after death from a liver abscess. It was suggested that heartbeat can interfere with diagnostic imaging and that it may be difficult to detect a solid tumor in

Table I. Antibodies for immunohistochemical staining.

Antibody	Clone	Dilution	Result	Supplier	Catalogue number
CK7	OV-TL 12/30	1:600	Positive	Novocastra	M7018
CK20	KS20-8	1:200	Negative	Novocastra	M7019
TTF-1	8G7G3/1	1:400	Negative	Labvision	M3575
CDX-2	EPR2764Y	RTU	Negative	Ventana	760-4380
p53	DO-7	1:400	Positive	Cellmarque	800-2912
AMACR	13H4	1:200	Negative	Dako	M3616
PSA	Polyclonal	RTU	Negative	Ventana	760-2506
S100 protein	Polyclonal	RTU	Negative	Ventana	760-2523

RTU, ready to use; CK, cytokeratin; TTF-1, thyroid transcription factor-1; AMACR, alpha-methylacyl-CoA racemase; PSA, prostate specific antigen.

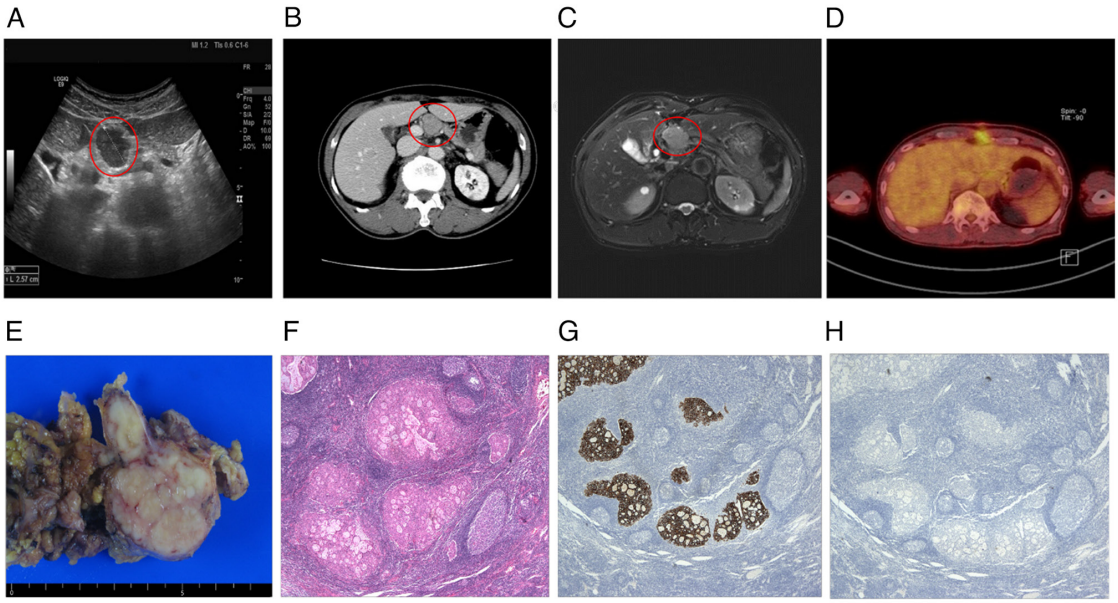

Figure 1. Hepatoduodenal ligament lymph node was initially diagnosed with cancer of unknown primary. (A) Ultrasonography showed a hypoechoic lymph node in the hepatoduodenal ligament, measuring ~2.7 cm (red circle). (B) Axial CT (venous phase) demonstrated hepatoduodenal ligament lymph node measuring 2.7 cm anterior to the common hepatic artery with no demonstrable hepatic mass (red circle). (C) Axial T2-weighted, fat-suppressed magnetic resonance imaging of the same metastatic lymph node revealed homogeneous hyperintensity (red circles). (D) Positron emission tomography/CT post-lymphadenectomy revealed mild diffuse FDG uptake in the midline of the abdominal wall and hepatoduodenal area, indicating postoperative change. No other notable FDG uptake was observed. (E) Cut surface of the metastatic lymph node had a pale yellow and granular appearance. (F) Hematoxylin and eosin staining of the lymph nodes showed the presence of metastatic adenocarcinoma cells with glandular differentiation. Immunohistochemistry for (G) CK7 was positive (x40) and (H) CK20 was negative (x40). CT, computed tomography; FDG, fluorodeoxyglucose; CK, cytokeratin.

the subphrenic area of the lateral segment of the liver. There are two patterns of lymph node metastases from the left lobe: Metastasis to lymph nodes in the hepatoduodenal ligament (regional lymph nodes) and around the cardiac portion of the stomach or along the common hepatic artery (distant lymph nodes), termed skip metastasis (10). Conway *et al* (4) reported iCCA in 24 (10.5%) of 228 CUP cases. The majority of these cases had radiographic satellite liver nodules and half of the patients showed vascular encasement. Cases of liver capsular retraction and intrahepatic bile duct dilatation have also been reported (4,11). CUPs have the potential to be diagnosed as iCCA; however, the lack of specific immunohistochemical biomarkers for iCCA diagnosis and rarity of CUP contribute to its misdiagnosis.

The most common sites of lymph node metastases in iCCA are pericholedochal, periportal and common hepatic artery lymph nodes (12). Regional lymph node metastases involving the hilar, periduodenal and peripancreatic nodes are considered N1 diseases with a IIIB TNM stage according to the American Joint Committee on Cancer eighth edition (13). The present patient was a representative case of iCCA of the left hemiliver with regional hepatoduodenal lymph node metastasis. In Japan, a study of 70 patients with iCCA reported that a hepatoduodenal lymph node may be a sentinel lymph node of iCCA (14). Lymph node metastasis is a key prognostic factor of iCCA. This occurs in up to 33% of early-stage tumors and typically precludes surgery (15). Lymph node metastases following iCCA resection are associated with a median overall

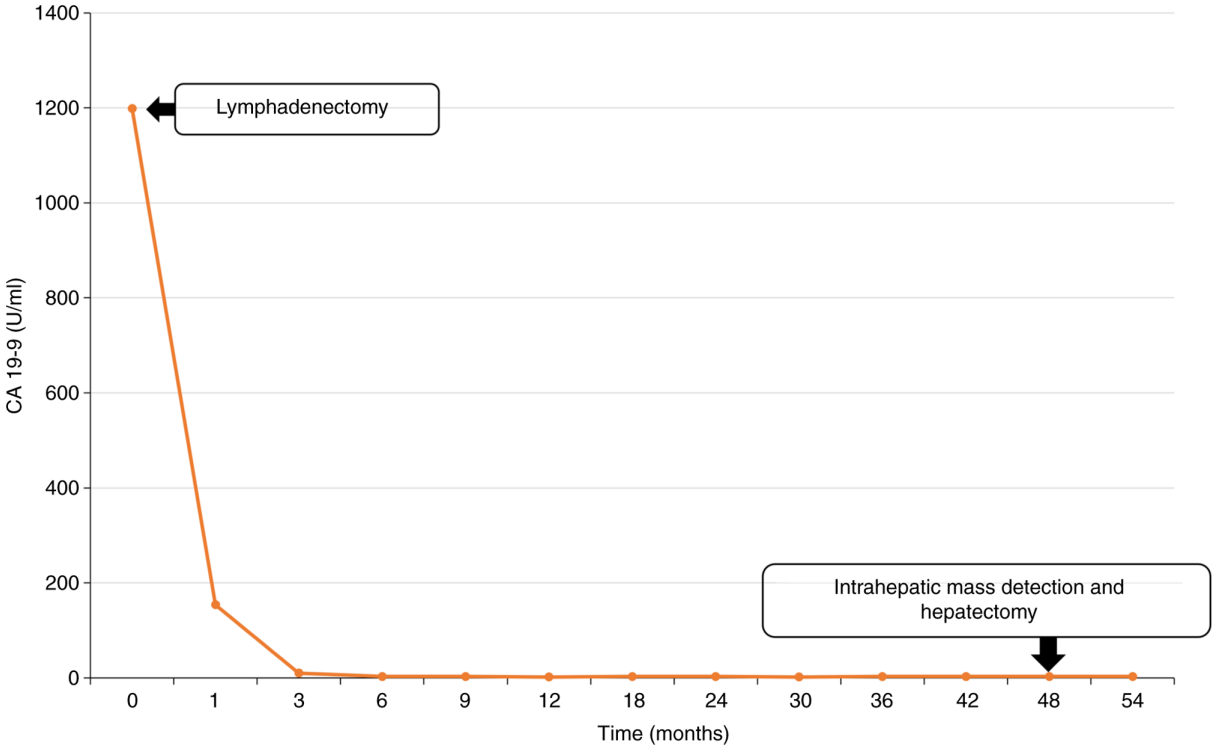

Figure 2. CA 19-9 levels before and after lymphadenectomy. After lymphadenectomy, elevated initial CA 19-9 values decreased and remained within normal range during the follow-up period. At the time of detection of an intrahepatic mass, CA 19-9 values were within the normal range. CA, cancer antigen.

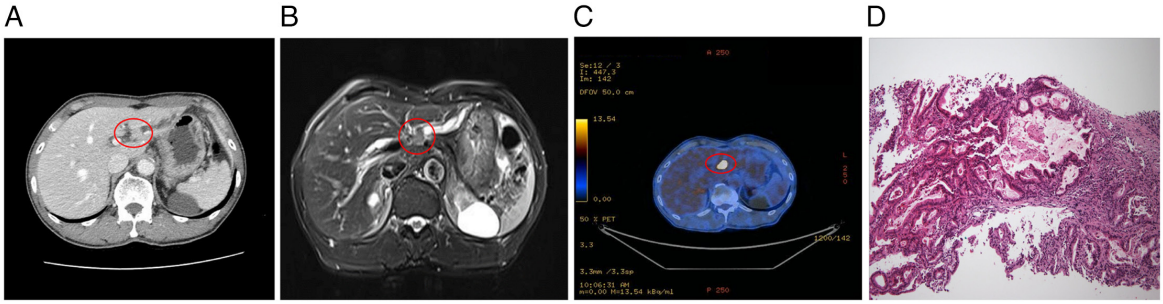

Figure 3. Delineated intrahepatic mass before radiotherapy. (A) Contrast-enhanced CT showed a intraductal solid mass measuring 1.1 cm in the left intrahepatic duct causing lobar bile duct dilatation (red circle). (B) Axial T2-weighted MRI demonstrated a 1.1 cm intraductal growing polypoid-enhancing mass within the dilated left hepatic ducts (red circle). (C) Positron emission tomography/CT showed a hypermetabolic lesion in the left lobe of the liver, also identified on CT and MRI. (D) Ultrasound-guided liver biopsy revealed a moderately differentiated adenocarcinoma with a focal papillary growth pattern following hematoxylin and eosin staining (magnification, x100). CT, computed tomography; MRI, magnetic resonance imaging.

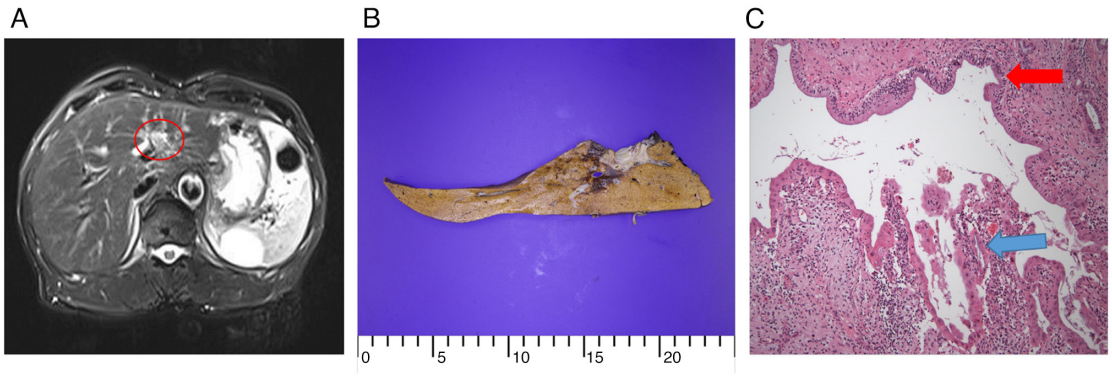

Figure 4. Resected liver specimen after radiotherapy. (A) Axial T2-weighted magnetic resonance imaging demonstrated an interval-marked reduction in the size of the previous intraductal polypoid lesion (red circle). (B) Gross specimen of resected liver showing a cavitary mass and periductal fibrosis with multifocal hemorrhage following radiation therapy. (C) Hematoxylin and eosin staining of normal bile duct epithelial (red arrow) and adenocarcinoma cells that responded to radiation therapy (blue arrow; magnification, x100).

survival (OS) of 15-22 months, which is less than half that of patients with node-negative disease (16-18). Martin *et al* (12) reviewed the National Cancer Database and evaluated patients with clinically node-positive iCCA treated with either resection- or chemotherapy-alone, or a combination of resection and chemotherapy; combined resection and chemotherapy is the optimal therapeutic approach with a median OS of 22.5 months vs. 11.9 months for chemotherapy-alone and 12.4 months for resection-alone. In addition, Jolissaint *et al* (19) reported that resection or hepatic arterial infusion chemotherapy significantly increases OS compared with systemic chemotherapy-alone in lymph node-positive disease. Therefore, resection is the first treatment option for patients with iCCA with lymph node metastasis.

Intrahepatic cholangiocarcinoma has three main growth patterns: Mass-forming, periductal-infiltrating and intraductal-growing. The mass-forming type is the most common and is characterized by intraparenchymal mass with distinct borders. The periductal-infiltrating type is characterized by tumor infiltration along the bile duct, often causing dilatation of the peripheral bile duct. Certain studies have shown worse survival after resection of the periductal-infiltrating type than the mass-forming type, whereas other reports have shown no difference in survival (20-22). The intraductal growth type is a slow-growing papillary tumor with a favorable prognosis compared with the other two types (11,23). Although the present patient was expected to have a poor prognosis due to early lymph node metastases and did not receive systemic chemotherapy, it was hypothesized that he had a relatively good prognosis with no distant metastases due to having the slow-growing intraductal growth type of the iCCA. iCCA is further classified into two main histological subtypes based on the level or size of the affected duct. Small bile duct iCCAs present as small tubular or acinar adenocarcinomas with nodular growth invading liver parenchyma, with no or minimal mucin production. Large bile duct iCCAs arise in large intrahepatic bile ducts and comprise mucin-producing columnar tumor cells arranged in a large duct or papillary architecture (1). In the present case, fibrosis and mucin accumulation were prevalent and scattered cancer cells were found focally in the resected liver specimen following radiotherapy. Owing to the effect of radiation, it was difficult to distinguish the three types of growth in the resected liver specimens. However, based on the US-guided liver biopsy specimen, the present case was considered to be of the intraductal growth type iCCA of the large duct. Serum CA 19-9 and CEA levels have been suggested to be independent risk factors for prognosis of cholangiocarcinomas, including iCCA (23).

The positivity rates for CA 19-9 (>37 U/ml) and CEA (>5 ng/ml) are 54.1 and 33.6%, respectively, in Japanese patients with iCCA (24). According to the clinical practice guidelines for iCCA of the Liver Cancer Study Group of Japan (LCSGJ), CA 19-9 and CEA are recommended as tumor markers for early detection and diagnosis of iCCA (25). In the present case, CA 19-9 was elevated at the time of the initial detection of lymphadenopathy and within the normal range at the time of the latent detection of the intrahepatic mass. Therefore, monitoring may be possible using imaging modalities, such as abdominal US, CT, and MRI, as well as tumor markers. Although tumor mutation profiling for treatment decisions for iCCA has not yet been established, patients with lymph node-positive iCCA with TP53 or KRAS mutation or cyclin-dependent kinase inhibitor 2A/B deletion have a worse prognosis than wild-type. Conversely, patients with isocitrate dehydrogenase 1/2 mutations exhibit no difference in survival compared with wild-type patients (19). Further analysis of tumor genetic alterations will provide information for assessing prognosis and selecting treatment options.

In conclusion, the present study reports a rare case of a definitively confirmed iCCA after a long-term follow-up of a patient who underwent resection for an incidentally detected lymphadenopathy in the hepatoduodenal ligament. Furthermore, it was suggested that surgical resection be performed when regional intra-abdominal lymphadenopathy is detected in the perihepatic region. iCCA of the left hemiliver should be considered as a differential diagnosis of primary tumors and monitoring should be performed. The present study may contribute to a better understanding of the pathophysiology and clinical course of ICCA, particularly of the intraductal growth type.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TL and SN conceptualized and designed the study. JRG and AH collected and analyzed radiological images. SN performed surgery and tissue collection. ML performed histopathological diagnosis. TL and AH interpreted the data and wrote the manuscript. TL and AH confirm the authenticity of all the raw data. All authors reviewed and edited the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Veterans Health Service Medical Center review board (Seoul, Korea; approval no. 2022-12-006). Written informed consent was obtained from the patient.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of details of their medical case and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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