Abstract. The present study reports a case of mass-forming intrahepatic cholangiocarcinoma (ICC), which mimicked cholangiocellular carcinoma (CoCC) during imaging and a needle biopsy examination. A 51-year-old female with no relevant medical history was referred to the National Defense Medical College hospital with an intrahepatic tumor. Computed tomography demonstrated non-homogeneous enhancement in the early arterial phase and persistent enhancement in the portal and equilibrium phases, together with notable swelling of the para-aortic lymph nodes. Gadolinium-ethoxybenzyl diethylenetriamine-pentaacetic acid-enhanced magnetic resonance imaging revealed low signal intensity in the hepatobiliary phase. The liver tumor and lymph nodes exhibited increased radiotracer uptake (maximum standardized uptake value=14.0) with positron emission tomography. A histological examination of a percutaneous needle biopsy specimen of the liver tumor indicated a diagnosis of CoCC. The patient underwent left hepatectomy and lymphadenectomy. The surgical specimen contained a poorly differentiated adenocarcinoma with anaplastic changes, which was immunohistochemically positive for epithelial membrane antigen (at the luminal membrane), cytokeratins 7 and 19, and negative for α-fetoprotein, hepatocyte-specific antigen, cluster of differentiation 56 and KIT. Based on these histopathological and immunohistochemical findings, the patient was diagnosed with ICC.

Introduction

Despite notable progress in the ability to preoperatively diagnose hepatic tumors due to recent technological advances in radiological imaging techniques, it may be difficult to obtain a precise preoperative diagnosis for liver tumors (1,2). Intrahepatic cholangiocarcinoma (ICC) has been reported to exhibit various imaging features such as irregular margins, thin peripheral arterial enhancement with progressive centripetal filling and delayed enhancement of the central portions, depending on the tumor’s location, size and intratumoral components (3). Additionally, computed topography (CT) findings in cholangiocellular carcinoma (CoCC) have demonstrated the histological features of the tumor (4). Furthermore, enhanced CT indicated the early enhancement and delayed washout of CoCC, similar to hepatocellular carcinoma (HCC) (5), or ringed enhancement at the periphery during the early phase and persistent enhancement during the delayed phase, similar to ICC on enhanced CT (6). Therefore, percutaneous needle biopsy examinations may be performed to diagnose liver tumors preoperatively. However, needle biopsy may yield different results depending on the region of the tumor that is biopsied due to the heterogeneous distribution of cells in liver tumors (7). The present study reports a case of mass-forming ICC, which mimicked CoCC during imaging and needle biopsy examination.

Case report

A liver tumor was incidentally located in a 51-year-old female during a medical check-up in September 2016. The patient had no significant medical, family, including with regard to genetic information, or psychosocial history of liver tumors. A routine physical examination produced normal results. No peripheral blood-, blood chemistry- or hemostasis-associated abnormalities were determined, except for a slightly elevated serum γ-glutamyl transpeptidase level of 63 U/l (normal range, <50 U/l). The patient’s tumor marker levels, including those of carcinoembryonic antigen [0.7 ng/ml (normal range,
<5.0 ng/ml], carbohydrate antigen 19-9 [7.5 U/ml (normal range, <37 U/ml)], α-fetoprotein [AFP; 4.3 U/ml (normal range, <20 U/ml)], and protein induced by vitamin K absence or antagonists-II [14 U/ml (normal range, <40 U/ml)] were within the normal limits. Abdominal ultrasonography revealed a 50-mm tumor in the lateral segment of the liver. Computed tomography (CT) demonstrated non-homogeneous enhancement in the arterial phase, persistent enhancement in the portal and equilibrium phases (Fig. 1A-D), and swelling and enhancement of the para-aortic lymph nodes. Gadolinium-ethoxybenzyl diethylenetriamine-pentaacetic acid-enhanced magnetic resonance imaging revealed low signal intensity in the hepatobiliary phase (Fig. 2A and B). Positron emission tomography/CT indicated fludeoxyglucose uptake by the liver tumor and lymph nodes (Fig. 3A-C). Due to the absence of underlying liver disease, elevated tumor marker levels and specific imaging findings, ultrasonography-guided percutaneous needle biopsy of the liver tumor was performed.

Histological examination of 10% formalin-fixed (24 h, room temperature), 3-µm paraffin-embedded sections was performed using hematoxylin-eosin (HE) and mucin staining. For HE staining, sections were stained with 0.12 g/v% hematoxylin solution produced by Hematoxylin (C.I. 75290) cryst. (cat. no. 104302; Merck KGaA, Darmstadt, Germany) three times (3 min/stain) at room temperature, and with eosin Y (cat. no. 058-00062; Wako Pure Chemical Industries, Ltd., Osaka, Japan) two times (1.5 min/stain) at room temperature. For mucin staining, sections were stained with Schiff’s Reagent (cat. no. 40921; Muto Pure Chemicals Co. Ltd., Tokyo, Japan) for 15 min at room temperature, and with Alcian Blue Stain Solution pH 2.5 for Histology (cat. no. 40852; Muto Pure Chemicals Co. Ltd.) for 20 min at room temperature. Staining was detected under a light microscope.

For immunohistochemistry, 10% formalin-fixed (24 h, room temperature), 3-µm paraffin-embedded sections were analyzed. The following commercially available primary antibodies were used: Anti-cytokeratin (CK)7 (cat. no. M7018; 1:200; Dako; Agilent Technologies, Inc., Santa Clara, CA, USA), CK19 (cat. no. M0888; 1:100; Dako; Agilent Technologies, Inc.), CK20 (cat. no. M7019; 1:100; Dako; Agilent Technologies, Inc.), glypican 3 (cat. no. 718021; Nichirei Bioscience, Inc., Tokyo, Japan), CEA (cat. no. A0008; 1:500; Dako; Agilent Technologies, Inc.), hepatocyte-specific antigen (cat. no. NCL-HSA; 1:50; Novocastra; Leica Microsystems GmbH, Wetzlar, Germany), epithelial membrane antigen (EMA; cat. no. M0613; 1:200; Dako; Agilent Technologies, Inc.) and KIT (cat. no. 713391; Nichirei Bioscience, Inc.). Briefly, sections were prepared as follows: For glypican 3 detection, samples underwent heat-induced epitope-retrieval [boiled at 100°C for 40 min in Heat Processor Solution pH 9 (cat. no. 715291; Nichirei Bioscience, Inc.); for CD56 detection, samples underwent heat-induced epitope retrieval [boiled at 100°C for 40 min in Heat Processor Solution pH 6 (cat. no. 715281; Nichirei Bioscience, Inc.)]; for CK7, 19 and 20 detection, samples underwent, proteinase-induced epitope retrieval [protease K (cat. no. 715231; Nichirei Bioscience, Inc.)] at room temperature (for 10 min). After blocking with 3v/v% hydrogen peroxidase solution (cat. no. 715142; Nichirei Bioscience, Inc.) for 5 min at room temperature, the sections were incubated with primary antibodies for 30 min at room temperature, followed by incubation with Histofine® Simple Stain MAX PO (MULTI) (cat. no. 724152; Nichirei Bioscience, Inc.) for 30 min, and finally with Histofine® Simple Stain DAB substance kit.
(cat. no. 725191; Nichirei Bioscience, Inc.; 5 min x2 incubations). The steps following incubation with primary antibodies were performed under a HISTOSTAINER 48A autostaining machine (Nichirei Bioscience, Inc.) at room temperature.

A histopathological examination of the biopsy specimen demonstrated spindle-shaped tumor cells with slightly eosinophilic cytoplasm and enlarged nuclei, arranged in a cord-like pattern. An immunohistochemical examination was performed according to the manufacturers' protocols; the results indicated that the tumor cells were positive for CK7 and glypican 3, partially positive for CD56 and negative for CK20, AFP, and hepatocyte-specific antigen (Fig. 4A-E). EMA staining revealed positivity in the luminal membranes of the tumor cells (Fig. 4F) (8,9). No mucus production was detected with Periodic acid Schiff-alcian blue (pH 2.5) staining. According to these findings, the patient was preoperatively diagnosed with CoCC (cT2N1M0 stage II, according to the eighth edition of the Tumor-Node-Metastasis Classification of Malignant Tumors developed by the Union for International Cancer Control) (10).

The patient underwent left hepatectomy and lymphadenectomy 72 days after her first visit to the National Defense Medical College Hospital. The regional lymph nodes, which were identified based on preoperative imaging and an intraoperative assessment, were removed. The regional lymph nodes were located in the hepatic hilum and hepatoduodenal ligament, posterior to the upper portion of the pancreatic head, and at the common hepatic artery and para-aortic stations. The operative time was 510 min, and the total amount of intraoperative blood loss was 721 g. The patient's postoperative recovery was uneventful, and she was discharged from the hospital on postoperative day 15.
The resected liver tumor measured 46x45x35 mm (Fig. 5A). The tumor was histologically composed of three parts: i) Polygonal eosinophilic carcinoma cells arranged in a cord- or nest-like pattern; ii) spindle-shaped carcinoma cells with an irregular growth pattern; and iii) a number of cancer nests with irregular tubular structures (Fig. 5B-D).
Additionally, mucin production was present in a portion of this tumor. This tumor did not exhibit histological features, and had admixtures of small monotonous glands, reflecting so-called antler-like anastomosing patterns as characteristics of CoCC (Fig. 6A). Immunohistochemical staining demonstrated that the tumor cells were diffusely positive for CK7 and CK19, positive for EMA (in the luminal membranes), and negative for HSA, CD56 and KIT. HSA, hepatocyte-specific antigen; CD56, cluster of differentiation 56; CK, cytokeratin; AFP, α-fetoprotein; EMA, epithelial membrane antigen; PAS, periodic acid-Schiff; CK, cytokeratin; HSA, hepatocyte-specific antigen; CEA, carcinoembryonic antigen; CD56, cluster of differentiation 56.

Table I. Comparison of histologic findings between needle biopsy specimen and surgical specimen.

| Special or immunohistochemical staining | Needle biopsy specimen | Surgical specimen | Characteristics |
|----------------------------------------|------------------------|-------------------|-----------------|
| PAS and/or alcian-blue                  | Mucin production (-)   | Mucin production (+) | ICC             |
| EMA                                    | Membranous positive    | Membranous positive |                |
| CK7                                    | Positive               | Positive           |                 |
| CK19                                   | Not determined         | Positive           |                |
| CK20                                   | Negative               | Negative           |                |
| CEA                                    | Not determined         | Negative           |                |
| AFP                                    | Negative               | Negative           | HCC            |
| HSA                                    | Negative               | Negative           |                |
| Glypican 3                             | Positive               |                   | Stem/progenitor cell |
| CD56                                   | Partially positive     | Negative           |                |
| KIT                                    | Negative               | Negative           |                |

ICC, intrahepatic cholangiocarcinoma; HCC, hepatocellular carcinoma; PAS, periodic acid-Schiff; EMA, epithelial membrane antigen; CK, cytokeratin; AFP, α-fetoprotein; HSA, hepatocyte-specific antigen; CEA, carcinoembryonic antigen; CD56, cluster of differentiation 56.

Figure 6. Histopathological analysis of resected liver tumor. (A) Hematoxylin-eosin staining demonstrated tumor cells with enlarged round nuclei and eosinophilic cytoplasm. Immunohistochemical staining of (B) CK7, (C) CK19, (D) EMA, (E) HSA, (F) glypican 3, (G) CD56 and (H) KIT demonstrated that the tumor cells were diffusely positive for CK7 and CK19, positive for EMA (in the luminal membranes), and negative for HSA, CD56 and KIT. HSA, hepatocyte-specific antigen; CD56, cluster of differentiation 56; CK, cytokeratin; EMA, epithelial membrane antigen (magnification, x20).

Additionally, mucin production was present in a portion of this tumor. This tumor did not exhibit histological features, and had admixtures of small monotonous glands, reflecting so-called antler-like anastomosing patterns as characteristics of CoCC (Fig. 6A). Immunohistochemical staining demonstrated that the tumor was positive for CKs 7, 19 (Fig. 6B and C) and EMA (Fig. 6D), and negative for AFP (Fig. 6E), hepatocyte-specific antigen, glypican 3, CD56 and KIT (Fig. 6F-H). EMA staining indicated that all of the tumor components in the resected specimen were cytoplasmic positive, but the normal liver was negative. This tumor did not exhibit characteristics of hepatic progenitor cells or stem cells. Based on these final histopathological and immunohistochemical findings, the tumor was diagnosed as a poorly differentiated ICC with anaplastic changes, not CoCC (Table I). The patient is still alive and has not suffered any recurrence at 15 months after surgery.
Discussion

ICC is the second most common type of primary liver cancer behind HCC in Japan in 2010 (1,11-16). A number of previous studies have reported rapidly rising rates of ICC over the recent decades globally (13,17). ICC has similar risk factors to HCC, including cirrhosis of the liver, chronic viral hepatitis, alcohol abuse, diabetes mellitus and obesity (18). As ICC exhibits various radiological features, including capsule retraction, satellite nodules, and peripheral biliary dilatation, depending on the tumor’s location, size, and intratumoral components (3,19), a definitive pathological diagnosis is required for appropriate treatment planning. However, CoCC is a rare type of primary liver cancer (20). There are a number of reports regarding the definition of CoCC. Recently, CoCC was classified as a stem-cell subtype of combined hepatocellular and cholangiocarcinoma (CHC) according to the 2010 World Health Organization classification (18,21). While, in Japan, CoCC was reclassified as a type of primary liver cancer according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer (9). Rules for the Clinical and Pathological Study of Primary Liver Cancer (9)

Table II. Histopathological features of CoCC and ICC.

| Histopathological features | CoCC | ICC |
|---------------------------|------|-----|
| Origin of tumor           | Cholangioles/ductules and the canals of Hering | Small intrahepatic bile ducts, including interlobular bile ducts |
| EMA immunohistochemical staining results | Membranous positive | Cytoplasmic positive |
| Mucus production          | Negative | Positive |
| Classification according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer (9) | An independent disease entity | ICC |
| World Health Organization classification 4th edition (21) | Subtype of CHC | ICC |

CoCC, cholangiocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; CHC, combined hepatocellular and cholangiocarcinoma; EMA, epithelial membrane antigen.

These data indicate that slow growth may be a characteristic of CoCC (28). Previous reports demonstrated CoCC primarily exhibited improved prognosis following resection, compared with ICC (20,29).

In the present case, a preoperative diagnosis based on a combination of imaging and pathological information was subsequently determined to be incorrect. The characteristic imaging findings of CoCC include a combination of early peripheral enhancement, the presence of intratumoral portal tracts, the absence of bile duct dilation and delayed contrast enhancement (5). However, the characteristic imaging findings of ICC include peripheral rim-like enhancement, central delayed enhancement, irregular tumor margins and capsular retraction (28,30). Therefore, the imaging findings of ICC are similar to those of CoCC. However, a number of hepatic tumors do not exhibit specific imaging findings. For example, the tumor in the present case exhibited HCC-like early enhancement in the arterial phase and ICC-like delayed enhancement in the portal and equilibrium phases; therefore, a percutaneous needle biopsy was performed. The biopsy specimen only included the part of the tumor containing spindle-shaped tumor cells with slightly eosinophilic cytoplasm and enlarged nuclei, which were arranged in a cord-like pattern. An immunohistochemical examination of the whole biopsy specimen demonstrated positive for CK7 and luminal EMA. However, the resected tumor revealed three distinct parts with different histological features, and an immunohistochemical examination indicated that the cytoplasm of the tumor cells was positive for CK7 and EMA. As was demonstrated in the present case, histopathological examinations of percutaneous needle biopsy samples do not always result in a correct diagnosis due to only small tumor samples being obtained (21). Intratumoral heterogeneity is increasingly recognized as a factor that has a major impact on diagnosis and the personalized treatment of a number of cancer types (3,19). A previous study indicated that ICC exhibits substantial intratumoral heterogeneity, which should be considered when producing therapeutic decisions based on single biopsy
Intrahepatic cholangiocarcinoma mimicking

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Authors' contributions

KN, TE and JY collaborated in the conception and design of

the study. KN, AK, MM, MN, MH, TN and SA acquired the

data. KN, TE, HTa, SO, YK, ES, YY, SH, HTs, KH, HU and

JY performed data analysis and interpretation. All authors

were involved in writing the manuscript. All authors read

and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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The patient provided written informed consent for the publica-

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Competing interests

The authors declare that they have no competing interests.

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