Cholangiocarcinoma at the Cystic Duct Discovered by Lymph Node Metastases with Clear Cell Transformation

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Abstract

We encountered a case with cholangiocarcinoma of the cystic duct, which was first manifested by multiple lymph node metastases with clear cell changes resembling clear cell adenocarcinoma (CCC). Because the clear cell changes were not prominent at the primary site, clear cell transformation might have occurred preferentially at the metastatic lesion in this case. Alternatively, tumor cells with clear cell transformation, found at the primary site, might have high metastatic potential. The patient showed thromboembolism and hypercalcemia as paraneoplastic syndromes at the terminal stage as reported in patients with CCC of the ovary. Those complications might be common biological features of CCC.

Key words: clear cell adenocarcinoma, cystic duct, lymph node metastasis

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Introduction

Clear cell adenocarcinoma (CCC) is a relatively rare cancer mostly found at the ovary or urinary tract. Although 10 cases with CCC generated from the gallbladder and extrahepatic bile duct were reported by Vardaman and Albores-Saavedra (1), CCC from the biliary tract is very rare. We describe a patient with cholangiocarcinoma of the cystic duct. Interestingly, the cancer was discovered by the multiple metastatic lesions of lymph nodes with clear cell transformation.

Case Report

A 74-year-old woman came to our hospital suffering from general malaise and weight loss. She had suffered for 4 months and had referred to her neighborhood medical practitioner. However, no disorder was found by routine examinations. When she came to our hospital, she was slightly anemic, and her bilateral cervical lymph nodes were markedly enlarged. Laboratory data showed mild anemia (RBC 374×10⁴/μl, Hb 9.5 g/dl, Ht 29.2%) and hypoproteinemia (Alb 3.0 g/dl), and serum tumor markers were elevated (CEA 7 ng/ml, CA19-9 467 U/ml). Although serum α-fetoprotein levels with specific lectin-binding properties have been reported to be elevated in such cases (1), they were not measured in the present case. Abdominal ultrasonography and CT scan showed a swollen gallbladder with a gallstone, and enlargement of multiple lymph nodes at the liver hilus, mediastinum, left axilla, and bilateral sides of her neck. CT scan, which was performed after dripped intravenous cholecysto-cholangiography, showed no flux of contrast medium into the gallbladder (Fig. 1A), and endoscopic retrograde cholangiography showed the interruption of contrast medium at the cystic duct (Fig. 1B), an obstructive lesion at the cystic duct was suspected. Gastrointestinal tract screening revealed gastric cancer. However, the lesion of the stomach was at an early stage. It was, therefore, not regarded as the primary site of the multiple lymph node metastases. Gallium scintigraphy showed abnormal uptake at enlarged lymph nodes. Therefore, a biopsy of the left cervical lymph

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Figure 1. (A) Computed tomography (CT) performed after dripped intravenous cholecysto-cholangiography. Because her gallbladder was not enhanced by the contrast medium (arrowheads) despite the fact that intrahepatic bile ducts were enhanced (broken arrows), an obstructive lesion around the cystic duct was strongly suggested. Enlargement of multiple abdominal lymph nodes was also observed (arrow). A schema for each CT image is shown in the inset. (B) Endoscopic retrograde cholangiogram performed to identify the primary site of the tumor. There were no abnormal findings in the common bile duct, but the contrast medium was interrupted at the cystic duct (arrow), and the gallbladder was not filled with contrast medium.

node was taken for a histological diagnosis. As shown in Fig. 2A, the histology revealed a cluster of CCC cells, which were strongly positive for CK7 and CK8/18, and were weakly positive for CK20 (data not shown). Although the cytokeratin profile was compatible with the tumor of bile duct origin, a tumor from the gastrointestinal tract, ovary, or urinary tract could not be excluded (2) although no tumor had been found by CT imaging. We, then, considered identifying the primary site of the tumor by probe laparotomy, but the patient and her family did not allow it. The size of cervical lymph nodes became greater, thereafter, and exudates followed. She suffered from cerebral embolism and hypercalcemia (calcium 12.7 mg/dl, parathyroid hormone-related protein 7.1 pmol/l, parathyroid hormone intact 9 pg/ml) at the terminal stage and died about one year from the onset of symptoms. Jaundice had not been recognized until one month before she died. Autopsy showed a large tumor with a cluster of lymph nodes at the middle to lower bile duct. Histological examination of the primary tumor showed moderately differentiated adenocarcinoma with partial clear cell transformation (Fig. 2B-D). Immunohistochemical study demonstrated the cytokeratin profile of the tumor cells at the primary site, in both non CCC and CCC lesions, was same as that of CCC cells of metastatic lesion (data not shown). In addition, pulmonary embolism was found in the right lung. However, there were no neoplastic changes in other portions except for the stomach, and the gastric lesion did not seem to progress for 8 months. Based on these findings, we finally diagnosed that the primary lesion of the tumor in this case was the cystic duct.

Discussion

CCC is a relatively rare cancer, which has been described in various anatomic sites (3). There are many reports on CCC of the ovary and urinary tract, but CCC of the extrahepatic bile duct is very rare. Vardaman and Albores-Saavedra reported 10 cases with CCC generated from the gallbladder and extrahepatic bile duct (1). In the present case, her cancer was discovered by the enlargement of systemic lymph nodes. The biopsy from her cervical lymph node was diagnosed as lymph node metastases of CCC, and the primary lesion was thought to be the tumor at the extrahepatic biliary tract based on the finding at autopsy. Moreover, because endoscopic retrograde cholangiogram had showed no significant findings in the common bile duct, the cystic duct was regarded as the primary site of metastatic CCC. However, because clear cell changes were not prominent at the pri-
Figure 2. (A) Histology of the biopsy specimen obtained from the enlarged cervical lymph node showed clusters of atypical cells with clear cytoplasm, which were rich in glycogen. The tumor was diagnosed as a lymph node metastasis of clear cell adenocarcinoma. (B-D) Autopsy findings. (B) A schema of macroscopic autopsy finding. Large tumor was observed in the middle to lower bile duct around the cystic duct (dotted area). (C) The tumor was located around the common bile duct and infiltrated into lymph vessels, veins, and peripheral nerves. A schema of the histological finding is shown in the inset. The structure of common bile duct (probably dotted line) was not well defined due to tumor invasion (dotted area). PV; portal vein. (D) The tumor was compatible with moderately differentiated adenocarcinoma in the biliary tree, and a part of the primary tumor showed a similar clear cell change just as that of cervical lymph nodes.

mary site, it might be possible that clear cell transformation preferentially occurred at the metastatic lesion of cholangiocarcinoma. Alternatively, tumor cells with clear cell transformation, which occurred at the primary site, might have high metastatic potential as reported in ovarian or renal cancer (4, 5).

Interestingly, jaundice was not revealed until she was in terminal condition. It could be due to slow growth of the tumor at the primary site, which is in contrast to the rapid growth of the metastatic tumor. Because clear cell change was more prominent in metastatic lesions than at the primary site and CCC cells are reported to have high malignant potential (4, 5), it could be possible that rapid growing CCC cells with high metastatic potential preferentially metastasized from the primary site, resulting in the slow growth of the primary tumor.

Immunohistochemical study showed that Hep Par 1 expression was recognized in both the primary and metastatic lesion in the present case. Cholangiocarcinoma is typically negative for Hep Par 1, which is a highly sensitive and specific marker for hepatocytes (6). However, Hep Par 1 is also reported to be stained in part of the metaplastic intestinal epithelium (7, 8), suggesting that clear cell transformation of cholangiocarcinoma might represent metaplasia to intestinal epithelium rather than to hepatocytes. Although the mechanism by which cytoplasm of the biliary cells becomes clear is unknown, it has been suggested that the accumulation of fat, acid mucin or distended endoplasmic reticulum could cause clear cell transformation (9).

During the course, she had accompanying hypercalcemia and thromboembolism as paraneoplastic syndromes. Among various ovarian tumors, CCC is reported to have a higher risk of thromboembolic complication compared with other histological types (4, 10). Although those complications tend to be seen in various cancers especially at the terminal stage, those might be common biological features of CCC irrespective of its embryologic origin.

In conclusion, we encountered a case of extrahepatic cholangiocarcinoma at the cystic duct with multiple lymph node metastases with clear cell transformation being predominantly recognized at the metastatic lesions. It may be possible that clear cell transformation preferentially occurred at the metastatic lesion, or tumor cells with clear cell transformation might have high metastatic potential. Because the
present case with CCC from the biliary tract showed similar complications as those from ovarian cancers, tumor cells with clear cell transformation may have common biological features irrespective of its embryologic origin.

References


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