Brain Metastases from Adenoendocrine Carcinoma of the Common Bile Duct: a Case Report

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INTRODUCTION

Most primary malignant neoplasms of the common bile duct are adenocarcinomas and composite tumors which are composed of plural histological tumors are not common. We report the first case of metastatic brain tumors from adenoendocrine carcinoma, one of composite tumors, of the common bile duct. In the present case both neuroendocrine carcinoma and adenocarcinoma were observed within the primary tumor.

CASE REPORT

A 68-year-old man had gradually developed headache and vomiting since April 1998. He became lethargic and was hospitalized in May 1998. Six years prior to admission, he had undergone surgery for cancer of the common bile duct. The size of the primary tumor was 6.0 x 4.5 cm and the histological diagnosis was adenoendocrine carcinoma. Three years prior to admission, the metastatic liver tumor had been totally removed. This metastatic liver tumor, measuring 11.0 x 10.0 x 7.0 cm in segments 3 and 4, was histologically neuroendocrine carcinoma without adenocarcinomatous component.

He developed right homonymous hemianopsia and mild cerebellar trunk ataxia. Laboratory examination revealed mild liver dysfunction, but tumor markers such as carcinoembryonic antigen (CEA), α-fetoprotein and squamous cell carcinoma-related antigen were all within the normal ranges. MRI of the brain revealed two solid heterogeneously enhanced masses in the left occipital lobe measuring 3.5 x 3.5 x 3.0 cm and in the cerebellar vermis measuring 2.5 x 2.5 x 3.0 cm without obstructive hydrocephalus (Figs 1 and 2). The tumor of the cerebellar vermis extended to the tonsils. Cerebral angiography showed two tumor stains supplied by branches of the left posterior cerebral artery and vermian branches of the posterior inferior cerebellar artery, respectively. On admission, no metastasis to the other organs could be seen on computed tomography (CT) scanning.

In May 1998 the brain tumors were completely resected in one stage. They were red in color and easily bleeding and had invaded the surrounding tissues. However, the ventricular wall of the fourth ventricle was intact.

The operative specimens of the common bile duct were stained using hematoxylin and eosin, the Grimelius (argyrophil) and
Figure 1. Preoperative MRI demonstrating a solid tumor in the cerebellar vermis without obstructive hydrocephalus. Coronal Gd-enhanced T1-weighted image showing a well enhanced tumor.

Figure 2. Three-dimensional spiral computed tomography (3DCT) demonstrating two enhanced tumors with surrounding vascular structures.

Fontana-Masson (argentaffin) methods. Microscopically the resected specimen of the primary tumor showed two components, well differentiated tubular adenocarcinoma and neuroendocrine carcinoma (Fig. 3A). Immunohistochemical examinations were performed to detect the presence of the antigens such as chromogranin A (CgA) (Dako, Glostrup, Denmark), neuron specific enolase (NSE) (Dako), synaptophysin (SYN) (Dako), glucagon (Dako), somatostatin (Dako), serotonin (Immunotech, Marseille, France), pancreatic polypeptide (Dako), CEA (Takara, Tokyo, Japan) and CA-19-9 (Dako) in the tumor cells. Each component of the adenoendocrine carcinoma showed distinctive immunoreactivities. Neuroendocrine markers such as CgA, NSE and SYN were diffusely detected in the neuroendocrine cells, whereas they were absent in the adenocarcinoma component. The Grimelius silver staining gave results overlapping those of CgA, whereas the Fontana-Masson argentaffin reaction was negative. The component of neuroendocrine carcinoma was positive for pancreatic polypeptide and serotonin, but negative for the remaining antibodies. In contrast, the adenocarcinomatous component was positive for CEA and CA19-9. These two components showed a transition between each other.

Microscopic examination of the metastatic brain tumors demonstrated neuroendocrine carcinoma without adenocarcinomatous component (Fig. 3B). These metastatic tumor cells were composed of small atypical cells with considerable atypia and frequent mitotic figures and were more malignant than the primary tumor. SYN- and serotonin-immunoreactive cells were detected like the metastatic liver tumor and primary tumor. However, in these metastatic brain tumors CA-19-9 and CEA-immunoreactive cells were recognized without glandular pattern (Fig. 3C and D).

The postoperative course was uneventful except for transient orthostatic hypotension. The patient's symptoms of increased intracranial pressure disappeared and his right hemianopsia improved markedly. He received postoperative radiotherapy at a dose of 50 Gy for these metastatic brain tumors. Eight months after the craniotomy, another two metastatic brain tumors were recognized on the follow-up MRI.

DISCUSSION

Tumors composed of a mixture of endocrine and exocrine cells have been recognized especially in the digestive tract. Such neoplasms have been referred to by a bewildering array of names, including goblet cell carcinoid (1), adenocarcinoid (2,3), mucin-producing carcinoid (4), argyrophilic mucin-secreting adenocarcinoma (5), composite carcinoid (6), composite carcinocarcinoid (7), adenoendocrine carcinoma (8) and amphicrine tumor (9). In the so-called adenoendocrine carcinoma two components are observed under the light microscopy; ordinary glandular carcinomas (adenocarcinoma) and neuroendocrine tumor. These tumors have been detected mainly in the stomach (10), small bowel (11), appendix and large intestine (7).

The histogenesis of mixed endo–exocrine tumors has not been fully explained. There are two hypotheses: (a) coincidental neoplastic change in two different cell types (12) and (b) neoplastic change of a single common precursor cell (7). In general, the morphology of metastatic tumors in adenoendocrine carcinoma is similar to that of the primary tumor. In the present case, the primary tumor was mainly composed of adenocarcinoma and partly of neuroendocrine carcinoma. In contrast, the metastatic tumors of the liver and the brain were mainly composed of neuroendocrine carcinoma which was more malignant than the primary tumor. As neuroendocrine carcinoma is considered to proliferate more rapidly, a discrepancy in the
Brain metastases from adenoendocrine carcinoma of the common bile duct

Figure 3. (A) Photomicrograph of primary tumor showing two components: well differentiated tubular adenocarcinoma and neuroendocrine carcinoma. These two components showed a histological transition between each other. H & E, original magnification x100. (B) These metastatic brain tumors were mainly composed of polygonal cells with round-to-elongated hyperchromatic nuclei and eosinophilic cytoplasm, which were compact or arranged in cords or ribbons. H & E, original magnification x100. (C) Immunohistochemistry for synaptophysin (SYN). Immunoreactivity for SYN is noted in the metastatic brain tumors, suggesting neuroendocrine cell differentiation. Original magnification x100. (D) Immunohistochemistry for serotonin. Approximately 5% of the metastatic brain tumor demonstrated serotonin-immunoreactive cells. Original magnification x100.

Histological features between primary and metastatic tumors may arise. A similar pattern of metastasis has been reported by Lyss et al. (3) and Varghese et al. (13). In the present case metastatic brain tumors also had CA-19-9 and CEA-immunoreactive cells without glandular pattern. This suggests that these metastatic tumors were composed of not only neuroendocrine cells but also adenocarcinomatous cells. Thus, the common origin theory is more compatible with the intricate admixture of different cell types and patterns within the primary tumor and metastases.

The endocrine cells demonstrated in the normal extrahepatic bile ducts are only somatostatin-containing D cells (14). In the present case, serotonin and pancreatic polypeptide were detected immunohistochemically, but somatostatin was not. These cells are considered to originate as part of a metaplastic process (15).

Ducla-Soares et al. (16) described the first case of an adenoendocrine carcinoma of the common bile duct. To our knowledge, the present report represents the second case of an adenoendocrine carcinoma in this location. Cases with metastatic brain tumor of adenoendocrine carcinoma are extremely rare. The prognosis of adenoendocrine carcinomas of the appendix and colon has been found to be worse than that of pure neuroendocrine tumors in the same location (2, 17). Early clinical results of colon cancer suggested that the presence of endocrine cells did not influence prognosis; however, recent results indicated that the concomitant existence of a significant neuroendocrine cell population seemed to worsen the prognosis (18, 19).

Although Ducla-Soares et al.'s patient with epiploon metastases was lost from the follow-up program 1 year after the surgery, our patient with liver and brain metastases was alive 6 years after the first surgery for primary tumor. Eight months after the craniotomy, however, another two metastatic brain tumors were recognized on the follow-up MRI. The neuroendocrine component may worsen the prognosis.

We hope that the concept of adenoendocrine carcinomas in the common bile duct will be discussed further.
References