A pure invasive micropapillary carcinoma of the pancreatic head: Long disease-free survival after pancreatoduodenectomy and adjuvant chemotherapy with gemcitabine [4]

Letter-to-the-Editor

Case report

A Pure Invasive Micropapillary Carcinoma of the Pancreatic Head: Long Disease-free Survival After Pancreatoduodenectomy and Adjuvant Chemotherapy with Gemcitabine

(Short working title: A Pure Invasive Micropapillary Carcinoma of the Pancreas)

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To the Editor:

Invasive micropapillary carcinoma (IMPC) first was described in the breast (1). The tumor cells are grouped in small cluster surrounded by a characteristic cleft (2). This type of cancer nearly always is associated with a poor prognosis and extensive lymph node metastases (3). IMPC of the ampullo-pancreatobiliary region has been reported only by Khayyata et al. (3), moreover, these tumors only rarely showed the clustered pattern exclusively.

We describe clinicopathologic and immunohistochemical features of a pure primary IMPC arising in the pancreatic head. Although we know of no previous report of effective adjuvant chemotherapy for IMPC, our patient's tumor responded completely to adjuvant chemotherapy with gemcitabine.

Case Report

A 67-year-old man, presented with obstruction of the transverse colon to another hospital, where a colonic tumor was resected surgically with tumor-free margins. As intraoperative exploration also disclosed a small area of induration in the gall bladder, cholecystectomy was performed simultaneously. The colonic tumor was macroscopically a type 4 cancer, with no accompanying ulceration. Initial pathologic diagnoses were "poorly differentiated adenocarcinoma, so-called linitis plastica type", and "metastasis to the gallbladder". However, since the tumor of the colon differed in appearance from typical colon cancer, this lesion was consistent with the possibility of carcinoma metastasis from

another organ. Three months after the first surgical treatment the patient complainted of general malaise, and became jaundiced. A pancreatic head tumor was detected by computed tomography (CT), and he was referred to our institution for additional treatment.

CT showed a nodular tumor in the head of the pancreas and multiple enlarged lymph nodes in the hepatoduodenal ligament. With administration of intravenous contrast material, enhancement of this tumor was poor in the early phase but relatively strong in the delayed phase ; the tumor margin was distinct. Magnetic resonance cholangiopancreatography (MRCP) showed expansion of the C-shaped duodenal loop around the pancreatic head. The lowermost common bile duct and main pancreatic duct were obstructed. Liver and lung metastases were not detected. Upper gastrointestinal endoscopy showed a elevated, eroded lesion surrounding the papilla of Vater, and a biopsy specimen from this lesion indicated adenocarcinoma. Initially, we diagnosed the pancreatic tumor as a recurrence of colon cancer representing mainly lymph node metastases, considering its expansile, nodular pattern of growth. As these findings argued against further surgical resection, we instead administered cisplatinum (CDDP) as a daily intravenous infusion from days 1 to 5 of chemotherapy, followed by cessation for two days. We continued this schedule for 1 month, but the outcome was progressive disease and signs of duodenal constriction appeared.

We decided upon palliative resection to reduce gastrointestinal symptoms. With the patient's informed consent we performed pancreatoduodenectomy, finding tumors in the remaining transverse and sigmoid colon in addition to the pancreatic tumor. We

simultaneously performed partial colectomy. The pancreatoduodenal reconstruction method was IIA.

Macroscopically, the tumor of the pancreas measured 45×55×35 mm, it had a soft consistency and was whitish to gray on cut section. The histologic pattern was characterized by small, round to ovoid micropapillary tumor cell clusters without fibrovascular cores, lying within clefts. In most areas the micropapillary clusters were closely packed, with scant intervening stroma. The cells had fairly abundent acidophilic cytoplasm, and showed moderate nuclear atypia (Fig. 1A). Focal lymphatic invasion was marked, and venous invasion was moderate. No area of typical adenocarcinoma was seen, with the tumor consisting purely of IMPC. Tumors of the colon and gallbladder showed the same findings limited to the submucosa, a pattern compatible with metastases from the pancreatic tumor.

MUC 1 immunostaining was prominent and diffuse along the surfaces of cell clusters facing the stroma (Fig. 1B). Immunohistochemically, the tumor was positive for cytokeratin (CK) 7 (Fig. 1C) and negative for CK20 (Fig. 1D). Tumor cells were positive for carbohydrate antigen (CA) 19-9 (Fig. 1E) and negative for carcinoembryonic antigen (CEA) (Fig. 1F).

Adjuvant systemic chemotherapy with gemcitabine was begun on the 40th postoperative day as a biweekly intravenous infusion of gemcitabine 30 over min (900 mg/m^2), with outpatient administration 36 courses. We examined for recurrence by CT every 3 months. At 42 months after surgical resection the patient was well with no sign of

recurrence when he died suddenly of accidental trauma. No neoplastic lesions were detected in other organs such as breast, lung, or urinary tract throughout the course.

Discussion

We report a unique case of a patient with a pure invasive micropapillary pancreatic carcinoma. After he received gemcitabine as adjuvant chemotherapy following pancreatoduodenectomy, he survived disease-free for more than 3 years.

Invasive micropapillary carcinomas have been associated with a high degree of aggressiveness, arising in various organs including breast, urinary bladder, lung, and colon, manifested by advanced stage at presentation, massive lymph node metastasis, and extensive lymphatic and vascular invasion. Ampullo-pancreatobiliary invasive micropapillary carcinomas have been reported to account for 4.1% of the carcinomas in this region (3). Extent of the micropapillary component in primary tumors has been classified by Khayyata et al. (3) as focal (20% to 50% of the tumor), predominant (51 to 80%), or diffuse (over 80%). Finding the diffuse type to be very rare, those authors reported only two such cases originating from the pancreas and two others originating from the periampullary region. Our case, a pure IMPC without areas of typical adenocarcinoma of the pancreas, needed to be distinguished from an IMPC that had metastasized to this region from another organ; invasive micropapillary carcinoma can be pure in metastases even when this pattern is only focally present in the primary tumor. Moreover, the IMPC morphology is not specific for any anatomic location.

In cases with periampullary origin, liver injury from biliary tract obstruction should be evident even at an early stage. In our case, liver injury was not apparent with a tumor mass in the pancreatic head could be demonstrated by CT.

In addition to clinical information, immunohistochemical stains such as CK7 and CK20 can be helpful in identifying the primary tumor site, since the CK7/CK20 immunohistochemical staining pattern usually is retained in both the primary IMPC and metastatic foci (2,4). IMPC of the breast, lung, and parotid gland all are CK7+/CK20-, as is micropapillary transitional cell carcinoma. IMPCs of the colon, however, are CK7-/CK20+ – as are typical colonic cancers. In our case the pancreatic tumor and the presumable metastatic tumors in the colon and gallbladder all were CK7+/CK20-. In addition, the tumors of colon and gallbladder had the same morphology as the pancreatic lesion as well as a distribution limited to the submucosa. These findings indicated that the colon and gallbladder tumors had metastasized from the pancreatic tumor.

MUC 1, a glycoprotein normally located at the apical cell surface of normal glandular epithelium, has an important physiologic role in maintenance of lumina and an inhibitory role in tumor cell-stroma interaction. In in vitro studies, increasing MUC 1 expression was associated with decreased adhesion between adjacent cells and between cells and the extracellular matrix (5). In typical carcinomas of the pancreas increased expression of MUC 1 was associated with low-grade cytologic features and good prognosis, while aberrant expression such as intracytoplasmic localization was associated with poor outcome

independently of tumor differentiation (6). In our case expression of MUC 1 in neoplastic cell clusters was present in the surface facing the stroma, as a narrow band of staining; significant lymphotropism was observed. IMPC, then, shows reversal of cellular polarity in an "inside-out" growth pattern where the surfaces of tumor cells that face the stroma acquire apical secretory properties. This has been demonstrated in earlier studies by electron microscopy (7) as well as immunohistochemical staining for MUC 1 (8). MUC 1, then may be an important factor in detachment of cells from the stroma, contributing to a micropapillary morphology as well as facilitating spread of cells by dissection of the stroma.

Gemcitabine (difluorodeoxycytidine) is a nucleoside analogue that is highly effective against typical pancreatic cancer (9). Gemcitabine was effective even in our IPMC case. Since this tumor originated from the pancreas, it may have retained some properties of typical pancreatic carcinoma, as verified by the CK7/CK20 immunohistochemical staining pattern. Characteristics of this tumor shared in common with typical pancreatic carcinoma may have readered it sensitive to gemcitabine, permitting disease-free survival for more than 3 years.

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Figure 1. Pathological examination. A、The histologic pattern of the pancreatic tumor. Hematoxylin and eosin, x200. B、Immunohistochemical analysis for MUC 1. Original magnification, x100. C、Immunohistochemical analysis for CK7. Original magnification, x100. D、Immunohistochemical analysis for CK20. Original magnification, x100. E、Immunohistochemical analysis for CA19-9. Original magnification, x100. Immunohistochemical analysis for CEA. Original magnification, x100.

Figure1

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