Mixed Ductal-Endocrine Carcinoma of the Pancreas

- A Case Report -

Ok-Jun Lee1 · Yong Mee Cho
Hyang-Im Lee · Duck Jong Han1
Jae Y. Ro

Department of Pathology, University of Ulsan College of Medicine, Asan Medical Center, Seoul; 1Department of Pathology, Chungbuk National University College of Medicine, Cheongju; 2Department of Surgery, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

Received: August 9, 2004
Accepted: October 4, 2004

Corresponding Author
Jae Y. Ro, M.D.
Department of Pathology, University of Ulsan College of Medicine, Asan Medical Center, 388-1 Pungnap-dong, Songpa-gu, Seoul 138-736, Korea
Tel: 02-3010-4550
Fax: 02-472-7988
E-mail: jaero@amc.seoul.kr

Key Words: Neoplasms, Complex and Mixed-Pancreas-Carcinoma, Ductal-Endocrine Gland Neoplasm-Immunohistochemistry

Pancreas consists of acinar, ductal and endocrine cells, which are corresponding to pancreatic tumors of acinar, ductal and islet cell phenotypes. Most pancreatic tumors are composed of single cell type, but there have been several reported cases of pancreatic tumors with two or more cellular components. Mixed ductal-endocrine carcinoma is a malignant epithelial tumor in which the ductal and endocrine carcinoma cells are intimately admixed in the primary tumor as well as in its metastasis, and the endocrine carcinoma cells comprise at least one third to one half of the entire tumor components.1 This tumor is also referred to as mixed carcinoid-adenocarcinoma, mucinous carcinoid tumor,2 or simply mixed exocrine-endocrine tumor.3 Mixed ductal-endocrine carcinoma may have amphicrine or intermediate cells showing dual differentiation, reflecting the common endodermal histogenesis. Mixed pancreatic tumors excluding exocrine carcinoma of the pancreas with scattered endocrine cells (SECs) are extremely rare. Here, we presented a case of mixed ductal-endocrine carcinoma of the pancreas with metastasis in the peripancreatic lymph nodes and the liver, and a review of the literature was made.

CASE REPORT

The patient was a 63-year-old woman who presented with progressive obstructive jaundice and a 6-kg weight loss. Her physical examination was within normal limits. Abnormal laboratory data showed the following values: glucose, 129 mg/dL (normal, 70-110 mg/dL); AST (SGOT), 57 IU/L (<40 IU/L); ALT (SGPT), 102 IU/L (<40 IU/L); alkaline phosphatase, 246 IU/L (40-120 IU/L); γ-GT, 144 IU/L (8-35 IU/L); total bilirubin, 4.6 mg/dL (0.2-1.2 mg/dL); direct bilirubin, 2.2 mg/dL (<0.5 mg/dL). The levels of amylase and lipase were within normal limits. Tumor markers including carcinoembryonic antigen (CEA) and CA19-9 were also normal. Abdominal computed
tomography displayed a 4.5 cm, irregularly shaped mass located in the head of the pancreas with distension of the common bile duct and gallbladder. No evidence of distant metastasis, lymph node enlargement or major vessel invasion was present. Under the clinical impression of pancreatic head cancer, the patient underwent a Whipple’s operation.

In the Whipple’s operation specimen, an ill-defined, solid tumor was present in the pancreatic head. The tumor involved the terminal part of the common bile duct and focally protruded into the ampulla of Vater in the duodenal wall. The proximal common bile duct and the main pancreatic duct were dilated. The tumor was solid, firm, granular and whitish tan with focal areas of necrosis, and measured 4.5 cm in the greatest dimension. Twenty peripancreatic lymph nodes, measuring up to 0.8 cm in the greatest dimension, were identified. Microscopically, the tumor consisted of two intimately admixed malignant ductal and endocrine components. Two components were closely intermingled, and there were also transitional foci between them (Fig. 1). The endocrine component comprised one-half of the tumor tissue that was composed of small round cells with an eosinophilic or clear cytoplasm. They had oval to round, hyperchromatic nuclei and arranged in solid and trabecular patterns (Fig. 2). The ductal component consisted of moderately differentiated adenocarcinoma with irregularly shaped infiltrating glands embedded in a desmoplastic stroma. The ductal carcinoma cells were columnar with a pale eosinophic cytoplasm, oval or round nuclei, and prominent nucleoli (Fig. 3). There was no evidence of acinar differentiation by light microscopy. The tumor infiltrated perineural spaces and peripancreatic fat. Three peripancreatic lymph nodes showed metastases and all three metastatic lymph nodes contained both ductal and endocrine carcinoma.

Fig. 1. Both ductal (arrow heads) and endocrine (arrows) carcinomatous components are closely intermingled, and there are transitional foci between them.

Fig. 2. The endocrine carcinoma cells have oval to round and hyperchromatic nuclei arranged in solid and trabecular patterns.

Fig. 3. The ductal carcinoma component comprises of irregularly shaped glands embedded in a desmoplastic stroma. The cells are columnar with pale eosinophic cytoplasm, oval or round nuclei, and prominent nucleoli.

Fig. 4. By immunohistochemistry, the endocrine carcinoma cells are reactive for synaptophysin, and the ductal carcinoma cells are reactive for carinoembryonic antigen (inset).
Mixed Ductal-Endocrine Carcinoma of the Pancreas

355

components.

The ductal adenocarcinomatous glands were stained for neutral mucin with positive reaction by periodic acid-Schiff stain. Immunohistochemically, the endocrine tumor component expressed pancytokeratin, chromogranin A and synaptophysin (Fig. 4), and the ductal tumor component expressed pancytokeratin, cytokeratin 7, carcinoembryonic antigen, and Leu M1. There was no expression for cytokeratin 20, insulin and glucagon in both tumoral components (Table 1).

**DISCUSSION**

Mixed ductal-endocrine carcinoma is characterized by an intimate admixture of ductal and endocrine carcinoma cells in the primary tumor as well as in its metastases. The mixed type metastasis is necessary for the diagnosis of mixed ductal-endocrine carcinoma. Tumors that are composed of two topographically separate components (collision tumor) are by definition not included in the mixed ductal-endocrine category. Scattered endocrine cells (SECs) have been reported to be present in exocrine pancreatic tumors, including ductal adenocarcinomas, intraductal papillary-mucinous tumors, mucinous-cystic tumors, acinar cell carcinomas, and pancreatic blastomas. Therefore, the endocrine cells of mixed ductal-endocrine carcinomas should comprise at least one third to one half of the tumor tissue. The ductal differentiation is defined by mucin production and the presence of ductal type marker such as CEA. The endocrine cells are characterized by the presence of general endocrine markers and/or hormonal products. This tumor may be derived from amphi-crine or intermediate cells which show dual differentiation.

Ductal adenocarcinomas with SECs should be included in differential diagnosis, since SECs are found in 40-80% of ductal adenocarcinomas. This phenomenon remains unclear whether SECs are neoplastic or not. Recent reports have suggested that these endocrine cells are non-neoplastic and derived from the surrounding islets, because SECs are associated with carcinomatous cells in primary tumors, but none of the metastases. Based on the above findings, mixed ductal-endocrine carcinomas could be distinguished from ductal adenocarcinoma with SECs according to the presence of endocrine cells in the metastatic sites.

The existence of mixed tumors with endocrine and exocrine differentiation raise the question of the relationship of endocrine and exocrine components in the pancreas. It is now considered that both are derived from the endoderm and arise from primitive precursor cells that are capable to differentiate to several directions, finally leading to the complex cellular composition of the mature pancreas. Depending on the potency of the precursor cell at the time of neoplastic transformation, the resulting tumor may either show pure endocrine, pure exocrine, or a spectrum of endocrine and exocrine differentiation.

Mixed ductal-endocrine carcinomas are exceptionally rare. So far only five cases that appear to fulfill the criteria given earlier have been reported in the English literature (Table 2). These tumors occurred in patients whose ages ranged between 62 and 74 years. Three patients complained of jaundice and/or weight loss. An endocrine manifestation of a Zollinger-Ellison syndrome was present in one case. Mixed ductal-endocrine carcinomas are often located in the pancreatic head. There are several other cases in the literature described “mixed pancreatic tumors”, but these cases do not fulfill the strict criteria of mixed ductal-endocrine carcinoma, as defined in the WHO Classification.

In this report, the patient was a 63-year-old woman, and her complaint was jaundice and weight loss with no evidence of endocrine manifestation. The tumor was present in the pancreatic head and both exocrine and endocrine components comprised

<table>
<thead>
<tr>
<th>Antigens</th>
<th>Ductal component</th>
<th>Endocrine component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancytokeratin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Carinoembryonic antigen</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Leu M1</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Cytokeratin 7</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cytokeratin 20</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Chromogranin A</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Synaptophysin</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Insulin</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Glucagon</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Table 1. Results of immunohistochemistry of mixed ductal-endocrine carcinoma**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sex/Age</th>
<th>Clinical findings</th>
<th>Size (cm)</th>
<th>Location</th>
<th>Site of metastasis</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eusebi 1981</td>
<td>M/65</td>
<td>Jaundice</td>
<td>6</td>
<td>Head</td>
<td>Liver</td>
<td>24 months</td>
</tr>
<tr>
<td>Sessa 1990</td>
<td>NA/62</td>
<td>NA</td>
<td>NA</td>
<td>Head</td>
<td>Liver</td>
<td>NA</td>
</tr>
<tr>
<td>Schron 1984</td>
<td>F/62</td>
<td>Jaundice, WL</td>
<td>10</td>
<td>Multiple organs</td>
<td>5 months Died,</td>
<td></td>
</tr>
<tr>
<td>Terada 1999</td>
<td>M/62</td>
<td>Zollinger-Ellison syndrome</td>
<td>3</td>
<td>Head, WL node</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Leteurtre 2000</td>
<td>M/74</td>
<td>Jaundice, WL</td>
<td>4.5</td>
<td>Head, WL node</td>
<td>Died, 24 years</td>
<td></td>
</tr>
<tr>
<td>Present case</td>
<td>F/63</td>
<td>Jaundice, WL</td>
<td>4.5</td>
<td>Head, WL node</td>
<td>Died, 5 months</td>
<td></td>
</tr>
</tbody>
</table>

NA, not available; WL, weight loss.

**Table 2. Reported cases of mixed ductal-endocrine carcinomas of the pancreas in the literature**
at least one-half of the tumor tissue. A significant amount of both ductal and endocrine components were also present in the metastatic sites in three peripancreatic lymph nodes. During the follow-up, hepatic metastasis was identified 2 months after diagnosis. The fine needle biopsy of hepatic mass showed only endocrine carcinomatous component. The patient died 5 months after the initial diagnosis.

This case fulfilled the criteria of mixed ductal-endocrine carcinoma and displayed typical clinical presentations and histologic features. The prognosis of mixed ductal-endocrine carcinoma is unclear at the present time because of its rarity. Although it is generally accepted that this tumor behaves like the usual ductal adenocarcinoma, the prognosis may depend on the proportion of the endocrine component. Experience with more cases and longer follow-up is needed to find out the clinical course of these tumors.

**REFERENCES**


