Rapidly Progressing Anaplastic Carcinoma of the Pancreas with Mucoepidermoid Carcinoma: An Autopsy Case Report

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Abstract:
A 75-year-old man visited our hospital for the examination of a tumor in the pancreas. Computed tomography showed an 85x85-mm low-density tumor in the pancreas. The tumor was pathologically diagnosed as poorly differentiated carcinoma by endoscopic ultrasound-guided fine-needle aspiration. Although we started chemotherapy, the patient died 84 days after the diagnosis. An autopsy demonstrated a ruptured anaplastic carcinoma with mucoepidermoid carcinoma of the pancreas. Anaplastic carcinoma with mucoepidermoid carcinoma is a very rare histologic subtype of pancreatic carcinoma, so pathological findings are important for predicting the patient’s prognosis. Physicians should be aware of this rare but fatal disease.

Key words: anaplastic carcinoma, mucoepidermoid carcinoma, pancreas

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Introduction
Pancreatic ductal adenocarcinoma (PDAC) remains a malignancy with a poor prognosis. Anaplastic carcinoma of the pancreas is a very rare histologic subtype of pancreatic carcinoma and is associated with greater aggression and poorer prognosis than common PDAC. Anaplastic carcinoma shows various morphologies, which include spindle-cell type, pleomorphic cell type and giant cell type (1). Anaplastic carcinoma accounts for 2-7% of all newly diagnosed pancreatic carcinomas each year (2).

Mucoepidermoid carcinoma of the pancreas is categorized as an adenosquamous carcinoma and is characterized by three kinds of cells: squamoid cells, mucinous cells and cells intermediate between ductal basal cells and polygonal epidermoid cells. It is most commonly seen in salivary glands and has a good prognosis. Mucoepidermoid carcinoma is also an uncommon histologic subtype of pancreatic carcinoma and is an extremely rare entity (3-7). Therefore, the malignant potential of mucoepidermoid carcinoma in the pancreas is unknown.

We herein report an autopsy case of anaplastic carcinoma with mucoepidermoid carcinoma of the pancreas with a rapid fatal course.

Case Report
A 75-year-old man visited his physician due to abdominal pain in July 2018. Because an abdominal ultrasound examination revealed a tumor at the pancreas, he was introduced to our hospital for a detailed examination in August 2018. He did not have a family history of carcinoma. He had consumed about 5 g/day of alcohol for 55 years and 20 cigarettes a day for 40 years.

On a physical examination, a hard-tender mass of approximately 5 cm in diameter was palpable in the upper abdominal region. The laboratory findings revealed elevation of white blood cell count, C-reactive protein and duodenal pancreatic monoclonal antigen type 2 along with mild anemia (Table). The serum levels of carcinoembryonic antigen and carbohydrate antigen 19-9 were within the normal ranges (Table).

Although computed tomography (CT) taken eight months earlier because of rib fracture had not revealed any abnormal findings in the pancreas, contrast-enhanced CT showed...
a rim-enhanced 85×85-mm low-density pancreatic tumor with irregular margins (Fig. 1A). The tumor had spread to the liver, stomach, celiac artery, portal vein and superior mesenteric vein. Endoscopic ultrasound (EUS) revealed a hypoechoic tumor with irregular margins, and EUS-guided fine-needle aspiration (EUS-FNA) was performed (Fig. 1B). The pathological findings showed numerous atypical cells, suggesting poorly differentiated carcinoma (Fig. 1C).

Although there was no distant metastasis, we diagnosed it as unresectable due to invasion to major vessels, including the celiac artery and portal vein. Chemotherapy with gemcitabine and nanovector-albumin-bound paclitaxel was initiated. In October 2018, abdominal CT revealed that the pancreatic tumor had grown to 150 mm in diameter. Distant metastases were detected in the para-aortic lymph nodes, liver and lung (Fig. 2A). In addition, the pancreatic tumor had further spread into the stomach and duodenum. Because an endoscopic examination revealed gastric invasion and gastric outlet obstruction (Fig. 2B), we inserted a self-expanding metallic stent endoscopically (Fig. 2C). Although there were no complications after stent insertion, bloating, anorexia, epigastric and back pain did not improve.

The patient fell into a coma following a rapid decrease in blood pressure and died in November 2018. Because of the rapid fatal course, we performed an autopsy with the consent of his family. The autopsy revealed that the tumor had grown to 200 mm in diameter and ruptured with massive bleeding (Fig. 3A). The cause of death was ascertained as

| Table. Laboratory Data at the First Visit to Our Hospital. |
|-----------------|-----------------|
| Hematology      | Serology        |
| WBC             | CRP             |
| Neutro          | 12,700 /μL      |
| Lympho          | 85.7 %          |
| RBC             | 8.59 mg/dL      |
| Hb               | 6.3 %           |
| Pt              | 752×10⁴ /μL     |
|                  | 10.8 g/dL       |
|                  | 18.7×10⁴ /μL    |

Biochemistry

| Coagulation | Tumor marker |
|-------------|--------------|
| Alb         | 3.7 g/dL     |
| T-bil       | 1.5 mg/dL    |
| AST         | 16 U/L       |
| ALT         | 15 U/L       |
| LDH         | 228 U/L      |
| ALP         | 229 U/L      |
| γGTP        | 233 U/L      |
| BUN         | 10 mg/dL     |
| Cre         | 0.72 mg/dL   |
| AMY         | 56 U/L       |
| LIP         | 27 U/L       |
| FPG         | 116 mg/dL    |
| HbA1c       | 5.8 %        |

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Figure 1. Contrast-enhanced computed tomography images at our hospital on day 1. An 85×85 mm low-density pancreatic tumor with high density area on the periphery of the tumor had spread to organs near the pancreas, such as the liver, stomach, celiac artery, portal vein and superior mesenteric vein (A). Endoscopic ultrasound revealed a hypoechoic mass with irregular margins (B). Pathological findings showed numerous atypical cells, suggesting poorly differentiated carcinoma (C).
hilaric shock as a result of spontaneous rupture of the pancreatic tumor. In addition, the pathological findings of the tumor showed that the tumor consisted of pleomorphic-type anaplastic carcinoma (Fig. 3B) composed of squamoid (Fig. 3C), intermediate (Fig. 3D) and mucinous cells (Fig. 3E). The proportion of mucoepidermoid carcinoma was a little higher than that of anaplastic carcinoma in the tumor. In addition, the metastatic lesions, para-aortic lymph nodes, liver and lung consisted mainly of mucoepidermoid carcinoma, with anaplastic carcinoma comprising only one part. Gene rearrangement and split signal were not detected by fluorescence in situ hybridization (FISH) using an isolated probe of the CTRC-MAML2 gene type.

Our final diagnosis was pleomorphic-type anaplastic carcinoma with mucoepidermoid carcinoma of the pancreas.

**Discussion**

We experienced a case of anaplastic carcinoma with mucoepidermoid carcinoma of the pancreas showing rapid tumor progression. Anaplastic pancreatic carcinoma is classified as a subtype of PDAC and is reported to potentially be a malignant transformation from PDAC (8). However, given that the present case contained no PDAC, it was possible that the tumor originally developed as an anaplastic carcinoma. Mucoepidermoid carcinoma is classified as a subtype of adenosquamous carcinoma, but little is known about its histonomy.

Both anaplastic carcinoma and mucoepidermoid carcinoma are very rare histologic subtypes of pancreatic carcinoma, and their prognoses are poorer than that of common PDAC (1, 3). The reported median survival time from the diagnosis of anaplastic carcinoma of the pancreas ranges from 3.3 months (9) to 12.8 months (10), which is significantly shorter than that of common PDAC. Mucoepidermoid carcinoma is most frequently seen in the salivary glands and is uncommon in the pancreas (11). There have been a few case reports of mucoepidermoid carcinoma of the pancreas, and the survival times were 2-45 months (5-7). The present case was resistant to treatment and had a poor prognosis.

It was reported that five patients underwent EUS-FNA for anaplastic carcinoma of the pancreas, and the cytology demonstrated anaplastic carcinoma in four and ductal carcinoma in one. The accurate diagnosis of anaplastic carcinoma was confirmed after surgical resection (12). The present case was difficult to diagnose using only EUS-FNA, because the amount of the specimen obtained for EUS-FNA was insufficient. Had the EUS-FNA specimen shown numerous atypi-
Figure 3. The autopsy revealed that the pancreatic tumor had grown to 200 mm in diameter and ruptured with massive bleeding (A). Pathological findings showed that the tumor consisted mainly of pleomorphic-type anaplastic carcinoma (B), while part of the tumor was composed of squamoid (C), intermediate (D), and mucinous cells (E).

cal cells, suggesting poorly differentiated carcinoma, the pancreatic carcinoma might have been deemed a rare histologic subtype of pancreatic carcinoma, like an anaplastic carcinoma with mucoepidermoid carcinoma.

CTRC-MAML2 translocation-positive mucoepidermoid carcinoma in salivary gland has been associated with good survival rates (13). However, the present patient with mucoepidermoid carcinoma had a rapid fatal course. Although the malignant potential of mucoepidermoid carcinoma in the pancreas is unknown, the CTRC-MAML2 translocation-negative status may have been the reason for the poor prognosis. The carcinoma’s pathologic aspects of poorly differentiated anaplastic carcinoma and high-grade mucoepidermoid carcinoma might have been responsible for the rapid fatal course in the present case.

There had been no abnormal findings on CT performed 8 months before admission in the present case, but a pancreatic tumor measuring 85 mm×85 mm was observed in the pancreatic body at the first visit. After 2 months, the tumor had grown to 150 mm in diameter. In a previous report on 9 patients with pancreatic carcinoma, the median doubling time was 144 days (14). Pathologically, the doubling time of pancreatic carcinoma with squamous component is 81.8 days, whereas that with an adenomatous component is 166.3 days (15). In the present case, the doubling time was 25 days, so the tumor grew rapidly and finally ruptured. Although whether or not the previous intratumor hemorrhaging had affected the rapid increase in the tumor size was unclear, the hematoma consisted of previous and new intratumor hemorrhaging. Pancreatic carcinoma with anaplastic carcinoma and mucoepidermoid carcinoma is one of the most lethal malignant neoplasms.

It is difficult to distinguish anaplastic carcinoma and mucoepidermoid carcinoma from the other types of pancreatic carcinoma without referencing the pathological findings. Regarding laboratory findings, some anaplastic carcinoma cases have shown severe anemia (hemoglobin level <10.0 g/dL), elevated white blood cell counts (>12,000/μL) and elevated serum carbohydrate antigen 19-9 levels (>37 U/mL) (16). The present case had an inflammatory response
and anemia, but the carbohydrate antigen 19-9 was within the normal range. Typical CT images of anaplastic carcinoma show a tumor with rim enhancement and central necrosis (17, 18). In the present case, the pancreatic tumor appeared as a low-density lesion with peripheral contrast enhancement without central necrosis on contrast-enhanced CT at the first visit. This made it difficult to distinguish anaplastic carcinoma from other types of pancreatic carcinoma. CT is also limited in its ability to distinguish mucoepidermoid carcinoma from other types of pancreatic carcinoma, because of its low specificity (3). EUS findings of anaplastic carcinoma of the pancreas show a hypoechoic and heterogeneous pattern (19), and the findings of mucoepidermoid carcinoma are hypoechoic pattern with slightly high internal echoes (11). In the present case, EUS revealed a hypoechoic mass with irregular margins, findings similar to those of common PDAC. Because it is difficult to distinguish anaplastic carcinoma and mucoepidermoid carcinoma from common PDAC, it is important to consider the possibility of this carcinoma and perform imaging examinations frequently when the pathological findings from EUS-FNA show poorly differentiated carcinoma.

In recent years, anaplastic carcinomas have been pathologically subdivided into three variants: pleomorphic type, spindle cell type and anaplastic carcinomas with osteoclast-like giant cells. The prognosis depends on the tissue type among cases of anaplastic carcinoma (19). Anaplastic carcinoma without osteoclast-like giant cells often cannot benefit from surgery, even if diagnosed in an operable state; however, anaplastic carcinoma with osteoclast-like giant cells may have a good long-term prognosis with surgical treatment (16). However, the effectiveness of chemotherapy for anaplastic carcinoma of the pancreas is still unknown for anaplastic carcinoma of the pancreas. The effectiveness of surgical treatment and chemotherapy for anaplastic carcinoma of the pancreas is still unknown. Although we started combination chemotherapy of gemcitabine and nanovector-albumin-bound paclitaxel according to the typical treatment approach for pancreatic carcinoma, the tumor grew in size.

Anaplastic carcinoma with mucoepidermoid carcinoma is a very rare histologic subtype of pancreatic carcinoma. The clinical diagnosis was difficult without pathological findings. Thus, a pathological examination was important for predicting the patient’s prognosis in the present case, and an autopsy was necessary to confirm the pathological findings because of the presence of various histological features. We should consider performing an autopsy when a patient has an unusual and rapid fatal clinical course.

**Conclusion**

We experienced a case of rapidly progressing anaplastic carcinoma with mucoepidermoid carcinoma of the pancreas. We should be aware of this rare fatal disease.

The authors state that they have no Conflict of Interest (COI).

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