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Case Report

A case of pancreatic mucinous cystic neoplasm accompanied by infiltrating anaplastic giant-cell carcinoma and literature review

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Abstract: This case was an old woman who had been suffering from peripancreatic space occupying lesions for more than 3 years. She underwent distal pancreatectomy and splenectomy. Under a microscopic examination, the tumor was composed of well-differentiated mucinous cystic neoplasm (MCN) and poorly differentiated anaplastic giant-cell carcinoma. Tumor giant-cells engulfing the neutrophils were visible in the region of anaplastic carcinoma. In terms of the immunophenotype of the neoplastic cell, CK, CK7, CA19.9 and Muc-1 were all positive; vimentin was partially positive, while CD20, CD3 and CD30 were all negative. The patient did not experience a recurrence at a 4-month follow-up. Pancreatic mucinous cystic neoplasm accompanied by infiltrating anaplastic giant-cell carcinoma is rarely reported. It belongs to a rare malignant pancreatic epithelial neoplasm, wherein the MCN maybe the limbo of anaplastic carcinoma, which ultimately transforms into anaplastic carcinoma.

Keywords: Pancreatic neoplasm, undifferentiated carcinoma, diagnosis, differential diagnosis

Introduction

Mucinous cystic neoplasm (MCN) of the pancreas originates from the exocrine pancreas, which does not communicate with the pancreatic ductal system and has characteristics of differentiation into gastroenteropancreatic epithelial cells [1]. Anaplastic pancreatic carcinoma (ANPC) is a very rare malignant pancreatic epithelial neoplasm, which mainly originates from the pancreatic duct and is a special type of neoplasm in nature. It has a high degree of malignancy and very poor prognosis. MCN is rarely found in clinics, and accounts for about 5.7% of the primary benign and malignant pancreatic neoplasms [2]. Meanwhile, MCN of the pancreas accompanied by infiltrating anaplastic giant-cell carcinoma is even rarer; only 13 cases have been reported in domestic and foreign studies. But MCN combined with anaplastic giant-cell carcinoma has not been reported yet. In this study, we retrospectively analyzed the clinical and pathological data of a case with MCN accompanied by infiltrating ANPCs. Also, we investigated its clinicopathologic manifestations, differential diagnosis and prognosis by combining domestic and foreign literature, thereby improving clinical understanding of the disease.

Case report

The patient was a 64-year-old woman. She was a Han farmer. She had suffered from hypertension for more than 30 years. Twelve years earlier, she underwent surgery due to intracranial aneurysm and showed good postoperative conditions. In terms of family history, her parents died of unknown reasons, and none of her other family members had similar diseases. She had also suffered from space occupying lesions of the pancreatic tail for more than 3 years and was admitted to our hospital due to intermittent abdominal pain for more than 10 days. CT revealed a quasi-circular low-density shadow in the pancreatic tail, with a size of 9.0 cm×7.9 cm, and a clear boundary, with visible segregation inside, slight calcification at the edge and progressive enhancement of lightness at the posterior edge. The pancreas showed natural co-

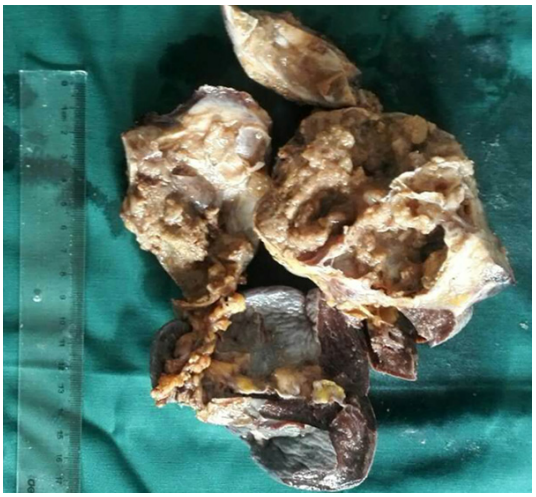

Figure 1. Gross specimen revealed a cystic-solid tumor with a gray sallow cross-section, in which a large amount of sticky matters and necrosis were visible. The cystic area appeared multilocular cystic, which there was mucus in the cyst.

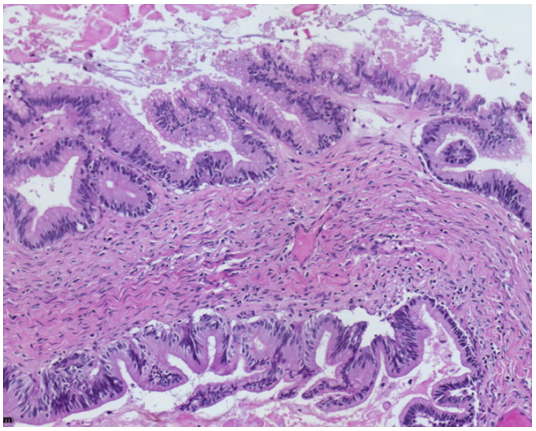

Figure 2. Cystic wall of mucinous cystic neoplasm (HE×40).

urse. The pancreatic duct was not significantly expanded, while abnormal density and enhancement shadows were also invisible. The patient was diagnosed with cystic lesions of the pancreatic tail, which was suspected to be cystadenoma. She underwent distal pancreatectomy and splenectomy. During the surgery, the tumor was found in the pancreatic tail, with a diameter of 10 cm and a smooth surface. It did not significantly adhere to surrounding organs. Liver protection, stomach protection, anti-inflammation, somatostatin and other symptomatic supportive treatment were administered on the patient postoperatively.

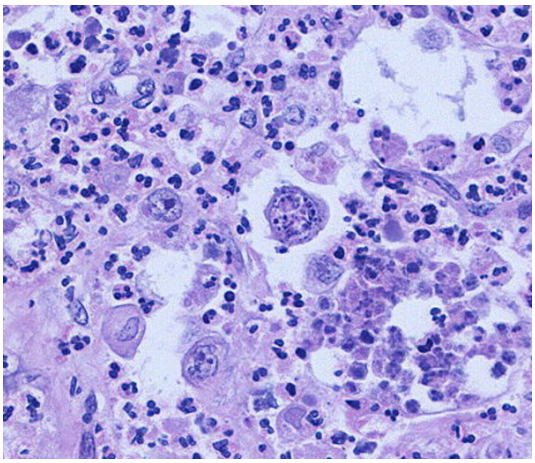

Figure 3. Neutrophils were visible in the tumor giant cells (HE×400).

Methods

Fresh specimens were fixed with 10% neutral formalin, followed by conventional dehydration, paraffin-embedding, sectioning into a thickness of 4 μm and HE staining. Immunohistochemical staining was performed using EnVision two-step method. All the primary antibodies, which included ER, PR, p53, p16, CA19.9, CK7, CK20, Muc-1, CD20, CD3, CD30, vimentin and ki-67, were purchased from Beijing Golden Bridge Biotechnology Co., Ltd. Staining was done according to the instructions on the reagents.

Visual observation

A pancreas sample, with a size of 10.0 cm×4.0 cm×1.5 cm, was sent for detection and a gray quasi-circular cystic solid mass was visible. It had a size of 8.5 cm×6.0 cm×3.0 cm, a gray-sallow cross-section and contained a large amount of sticky matter and necrosis. There was a spleen sample with a size of 12.0 cm×5.0 cm×3.5 cm, which had gray-red and soft cross-section but no obvious abnormalities (**Figure 1**).

Microscopy examination

One part of the tumor was a mucinous cystic neoplasm, which manifested as follow: the inner capsule wall was coated with mucinous epithelium, topical lesions were present on the papillary process and local epithelial nuclei were enlarged, showing obvious atypia. Mese-

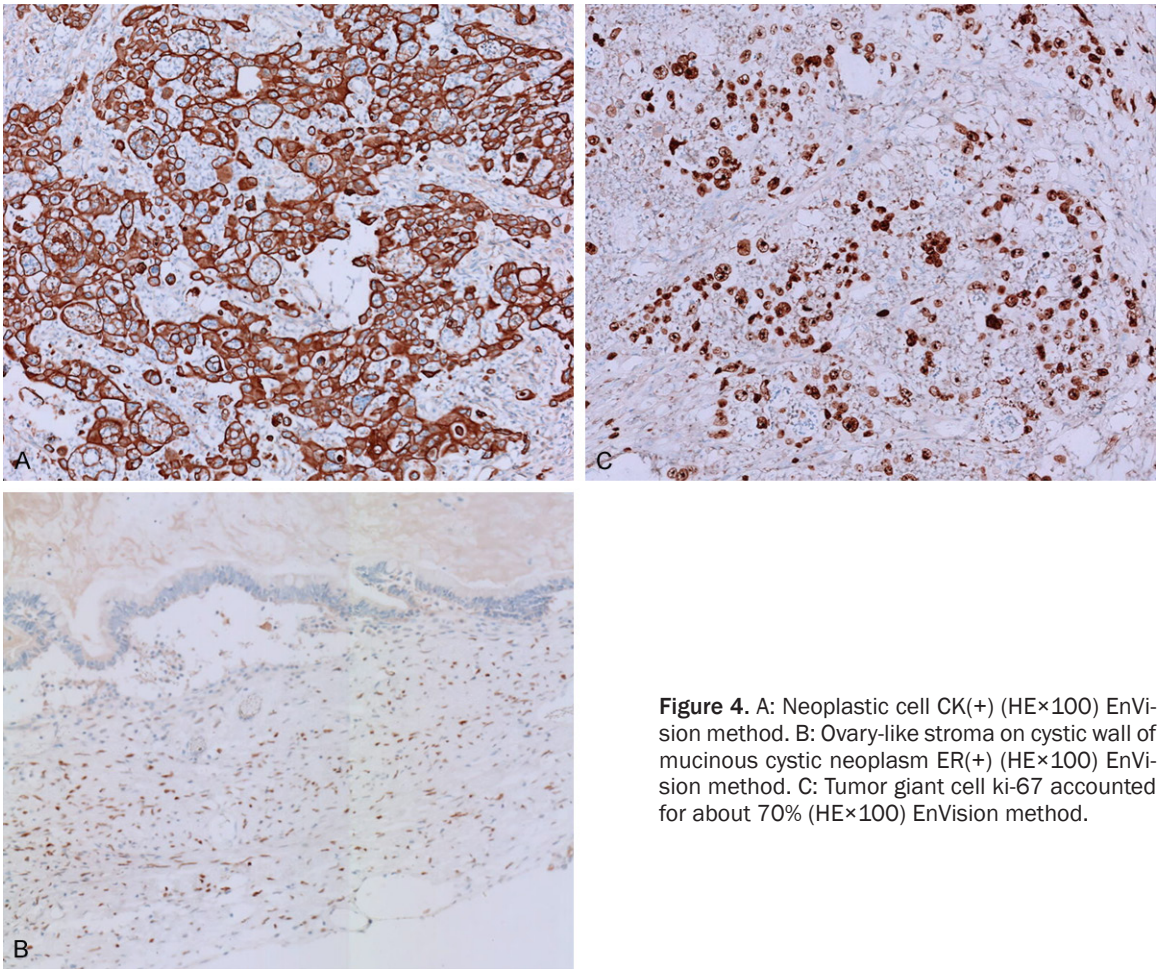

Figure 4. A: Neoplastic cell CK(+) (HE×100) EnVision method. B: Ovary-like stroma on cystic wall of mucinous cystic neoplasm ER(+) (HE×100) EnVision method. C: Tumor giant cell ki-67 accounted for about 70% (HE×100) EnVision method.

nchyme below the epithelium manifested as ovary-like mesenchyme with abundant cells (**Figure 2**). The other part of the tumor was undifferentiated carcinoma, which manifested as bulky cancer cells and significant polymorphism, with visible monocytes, binuclear cells and polykaryocytes, as well as easily visible nucleolus. There was neutrophils-dominated inflammatory cell infiltration in the mesenchymal tumor, and there were visibly engulfed neutrophils in the cytoplasm of part of the tumor giant-cells (**Figure 3**). There was no clear transition between these two parts after extensive sampling. There was a large amount of necrosis in the tumor, and significant mesenchymal fibrosis appeared in some regions. Meanwhile, no metastasis was found in the peripancreatic lymph nodes.

Immunophenotype

In the pleomorphic tumor giant-cells, CK, CK7, CA199 and Muc-1 were positive (**Figure 4A**); vimentin was partially positive, and subcutaneous mesenchyme of tumor capsule wall ER and PR were positive (**Figure 4B**). Tumor cell Ki-67 accounted for about 70% (**Figure 4C**), while other indicators, including CK20, CD20, CD3, CD30 and CDX-2, were negative.

Follow-up

The patient was followed up for 4 months and showed good conditions. No recurrence or metastasis was found in the primary and other sites.

Discussion

Compagno et al. [1] were the first to differentiate MCN from serous cystic neoplasm (SCN), and they put forward a suggestion that all the MCNs were malignant or potentially malignant. WHO divided it into non-infiltrating MCN and MCN accompanied by relevant infiltrating carcinoma. The former could be further divided into

low-middle grade dysplasia and high-grade dysplasia. A vast majority of MCN patients are female, with a male to female ratio of 20:1, and most of the sites are located at the pancreatic tail. ANPC belongs to the non-neuroendocrine neoplasm of the pancreas and has a low incidence, which only accounts for about 0.5% to 7% of all malignant exocrine tumors of the pancreas [3, 4]. WHO has classified ANPC as a subtype of ductal carcinoma of the pancreas. In addition, ANPC is also known as pleomorphic carcinoma, pleomorphic large cell carcinoma, spindle cell carcinoma and sarcomatoid carcinoma. It has a higher incidence in male than in female, and has a peak period ranging from ~70 to 90 years old, showing a very poor prognosis. Meanwhile, ANPC accompanied by MCN is very rare.

Clinical characteristics

The clinical symptoms of MCN depend on the neoplasm size. Smaller neoplasms (<3 cm) are mostly found accidentally in X-ray and surgery. Larger neoplasms often appear as secondary symptoms due to compression of the surrounding organs and manifest as abdominal pain and abdominal mass. Occasionally, cases with obstructive jaundice can be found, which is because MCN often occurs at the pancreatic tail and does not communicate with the secretory duct of the pancreas. However, in individual cases, the neoplasms form a sinus with the common bile duct, which allows a large amount of mucus to flow into the common bile duct and, thus, leads to obstructive jaundice. The main symptoms of anaplastic pancreatic carcinoma include nausea, abdominal pain, sore waist and aching back, emaciation and acratia, and other non-specific manifestations. However, it may also be accompanied by jaundice and vomiting. Signs manifest as an occasional palpable mass at the left upper abdomen, with or without tenderness. B-ultrasound or other imaging examinations such as CT and MRI often prompt pancreatic lesion, with the absence of other specific indicators. Laboratory examination may show increased serum CA19.9 level. The case in this study lacked specific clinical manifestations, imaging characteristics and laboratory examination indicators, which led to difficulty in preoperative diagnosis, and the ultimate diagnosis relied on pathological examination and immunohistochemistry.

Pathological characteristics

WHO classified undifferentiated carcinomas of the pancreas into three histologic subtypes: sarcomatoid carcinoma, carcinosarcoma and anaplastic giant-cell carcinoma. Sarcomatoid carcinoma is dominated by spindle cells; carcinosarcoma is composed of adenocarcinoma and high-grade spindle cells, while anaplastic giant-cell carcinoma consists of pleomorphic mononuclear cells and giant cells with oxyplasm. The case in this study suffered from anaplastic giant-cell carcinoma. In general, anaplastic carcinoma does not have a clear pancreatic ductal differentiation and mostly manifests as a solid nest growth pattern. This case manifested as atopical mucinous cystic neoplasm region. Transformation mechanism of pancreatic MCN accompanied by infiltrating anaplastic giant-cell carcinoma has not been elucidated yet. Currently, studies [5, 6] have pointed out that K-ras gene mutation rate in undifferentiated neoplasms was comparable to that in ductal adenocarcinoma. Meanwhile, K-ras 12^{th} exon mutation was also found in non-infiltrating and infiltrating MCN. Thus, we infer that MCN and ANPC may both originate from the pancreas ductal epithelium, while mucinous cystadenocarcinoma as an interim stage of transition to undifferentiated carcinoma will ultimately transform into the undifferentiated carcinoma, but the transformation mechanism is still known. In addition, we observed a massive neutrophil infiltration in the mesenchymal neoplasm as well as tumor giant-cells engulfing the neutrophils in the pancreatic undifferentiated carcinoma. These phenomena have not been reported yet, but are similar to the phenomenon of tumor giant-cells engulfing neutrophils in giant-cell carcinoma of the lung. We speculate that they have the same mechanism. Some scholars put forward the theory of tumor microenvironment and are of the view that tumor tissues could produce chemokines, which enables the neutrophils in the blood to pass through the vessel wall and enter the tumor tissues. These infiltrating neutrophils are called tumor-associated neutrophils (TAN) [7]. In recent years, many studies have demonstrated that TAN induced under tumor conditions plays an important role in the incidence and development of tumors. In tumor microenvironment and under the influence of different cytokines, TAN phenotype can cause polarization,

which can polarize into N1 type, inhibiting tumor growth, and into N2 type, promoting growth and metastasis of tumors [8, 9]. In addition, it is also believed that in giant-cell carcinoma of the lung, the tumor secretory chemokines can recruit neutrophils to lung tissues, and these neutrophils can promote lung metastasis [10].

Differential diagnosis

(1) Intraductal papillary mucinous neoplasms (IPMNs): Most of these neoplasms are located at the pancreatic head and communicate with the main pancreatic duct. Meanwhile, pancreatic MCN is mostly located at the pancreatic body and tail. Generally, IPMNs are accompanied by a large amount of mucus accumulation in the duct, which leads to significant ductal dilation, while MCN does not have such manifestations. Findings by microscopy reveals that there is no ovary-like mesenchyme surrounding the IPMN duct, and the mesenchyme surrounding the duct is unlikely to express ER and PR. However, MCN has opposite manifestations, and the neoplasm generally does not involve the pancreatic duct system. (2) Malignant fibrous histiocytoma: This kind of tumor is occasionally found in the pancreas. Histologically, it is composed of fibroblast-like spindle cells that are arranged in storiform pattern and a large number of circular or oval histiocyte-like cells. Mesenchymal tumor is mainly composed of collagen fibers containing abundant vessels and mucoid degeneration region and inflammatory granulation-like tissue region are partially visible. In the multinucleated giant-cell region of the neoplasm, CD68 is positive, while AE1/AE3 is negative [5]. Meanwhile, in multinucleated giant-cells of the ANPCs, CD68 is negative, while AE1/AE3 is positive. (3) Giant-cell carcinoma of the lung metastasizing to the pancreas: Differentiation is needed since both carcinomas are composed of mononuclear and polynuclear giant-cells, and both show the phenomenon of tumor cells engulfing neutrophils. The differentiation can be achieved by combining the clinical symptoms, signs, imaging and laboratory examinations as well as immunohistochemistry (TTF-1, CA19-9), where TTF-1 is (+) while CA19-9 is mostly (-) for cases with Giant-cell carcinoma of the lung metastasizing to the pancreas. (4) Anaplastic large-cell lymphoma: The pleomorphic tumor giant-cells in this ANPC patient are prone to be confused with the anaplastic large and middle tumor cells based on their morphology. Their differentiation is mainly based on immunohistochemistry, where tumor giant-cells, LCA and CD30, in anaplastic large-cell lymphoma are positively expressed, while the tumor giant-cells, CD30, in ANPCs are negative. (5) Malignant melanocytoma: This kind of carcinoma has diverse morphologies. It can exhibit giant mononuclear and polynuclear abnormal cells and has cytoplasmic polychromasia. Thus, it is prone to be confused with ANPC in morphology. However, histologically, the cytoplasm of malignant melanoma cells is generally reddish. The nuclei are deviated and possibly have red nucleolus, thus, forming pseudo-inclusion-like structure. In terms of immunohistochemistry, they can be differentiated by means of HMB45, MelanA and S-100. They are generally positively expressed in malignant melanocytoma but are negatively expressed in ANPC.

Treatment and prognosis

Undifferentiated carcinomas of the pancreas have very poor prognosis. Currently, there is still a lack of satisfactory treatment for pancreatic MCN accompanied by infiltrating anaplastic giant-cell carcinoma. Surgical resection is the main method of treatment for this kind of carcinoma, with chemotherapy if necessary. The patient in this study showed very good conditions during follow-up at 3 months postoperation, with the absence of recurrence and metastasis.

Disclosure of conflict of interest

None.

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