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An osteoclast-like giant cell tumor embedded in the mural nodule of a pancreatic mucinous cystic neoplasm

A case report and literature review

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Abstract

Rationale: Mucinous cystic neoplasms (MCNs) are relatively rare lesions, accounting for 2%–5% of all exocrine pancreatic neoplasms. MCNs mainly occur in women (female:male ratio = 20:1), with a peak incidence in the 5th decade of life. Osteoclast-like giant cell tumors (OGCTs) are rare and relatively aggressive neoplasms, comprising <1% of all pancreatic carcinomas. Herein, we present a rare "combination tumor" case and discuss the impact of mural nodules in pancreatic MCNs considering malignant transformation.

Patient concerns: A 54-year-old Mongolian man, without vomiting, nausea or jaundice, presented with abdominal distention since 3 months. He had a 7-year history of diabetes. Physical examinations indicated slight middle abdominal tenderness without rebound tenderness or rigidity. Laboratory results revealed that the level of carcinoembryonic antigen (CEA) was 1.16 ng/ml (normal: <5 ng/ml); CA-199: 30.02 U/ml (normal: <27 U/ml); hemoglobin: 143 g/L; fasting glucose: 7.71 mmol/L; and albumin: 43 g/L. Abdominal enhanced computed tomography revealed a 7 × 6 cm solid neoplasm in the pancreatic body with partial enhancement and heterogeneity. Endoscopic ultrasound revealed a solid-cystic space-occupying lesion in the pancreatic body.

Diagnosis: The preoperative preliminary diagnosis was pancreatic solid-cystic tumor, possibly a solid pseudopapillary tumor. Postoperative pathological findings revealed a pancreatic borderline MCN with an OGCT embedded in a mural nodule of the capsule. Immunohistochemical results indicated a simultaneous dual origin from the epithelium and stroma.

Interventions: The patient underwent open distal pancreatectomy and splenectomy. Postoperative blood glucose levels were closely monitored and regulated. We intravenously administered single-agent gemcitabine (1400 mg on day 1) as the first-time chemotherapy, 1 month after surgery. After the first chemotherapy, the patient refused to receive further treatment owing to personal reasons.

Outcomes: The patient showed uneventful recovery and was discharged 13 days after the initial surgery. Follow-up was performed 1, 3 and 6 months after surgery. At 6 months, abdominal computed tomography scan showed no signs of recurrence, regional lymphadenopathy, or other abnormalities. And laboratory tests showed a platelet count of 301×10^9/L, postprandial blood glucose of 12.9 mmol/L and CA-199 level of 20 U/ml. The patient had no obvious discomfort.

Lessons: Although pancreatic MCNs are widely accepted as borderline tumors, malignant transformations may occur due to various risk factors (cyst size, mural nodules, septations, and tumor location). The combination tumor in this case was more likely to increase the possibility of malignant biological behavior, thereby worsening overall prognosis. Therefore, long-term follow-up must be maintained with strict monitoring.

Abbreviations: CA199 = carbohydrate antigen 19-9, CEA = carcinoembryonic antigen, HGD = high-grade dysplasia, IGD = intermediate-grade dysplasia, IPMN = intraductal papillary mucinous neoplasm, LGD = low-grade dysplasia, MCN = mucinous cystic neoplasm, OGCT = osteoclast-like giant cell tumor, PCN = pancreatic cystic neoplasm, RBC = red blood cell, WBC = white blood cell, WHO = World Health Organization.

Keywords: malignancy ratio, mucinous cystic neoplasm (MCN), mural nodule, osteoclast-like giant cell tumor (OGCT)

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1. Introduction

Mucinous cystic neoplasms (MCNs) of the pancreas are a type of pancreatic cystic neoplasm (PCN). Over 90 percent of the cases are observed in women aged 40–60 years.[1] In most cases, nonmucinous PCNs are benign whereas 10%–15% of mucinous PCNs (mainly MCNs and intraductal papillary mucinous neoplasms) have some potential for malignancy.[2] However, it is extremely difficult to distinguish between PCN subtypes using only computed tomography (CT) or other imaging examinations. Several characteristics of MCNs, such as cyst size and mural nodules, are often associated with the grade of malignancy.

An osteoclast-like giant cell tumor (OGCT) is a rare and relatively aggressive neoplasm, and is one of the three types of pancreatic giant cell tumors, the other two types being pleomorphic and mixed tumors. The World Health Organization (WHO) has grouped these tumor types together as pancreatic undifferentiated carcinoma since 2010.[3] However, the osteoclastic-like variant may have a relatively better prognosis than the other two subtypes, as well as pancreatic adenocarcinoma.[4] Giant cell tumors have also been reported in other organs, including the breasts, thyroid, parotids, colon, skin, orbit, kidneys, heart, and soft tissue.[5–7] However, till date, there have been few reports of simultaneous occurrence of MCNs and OGCTs in one mass. Therefore, herein, we present a case of OGCT embedded in a mural nodule of a borderline pancreatic MCN.

2. Case presentation

A 54-year-old man presented with a 3-month history of middle abdominal distending pain without any irritation or radiating pain, although the discomfort would aggravate after meals. Different postures did not influence his condition, and he had no symptoms of vomiting, nausea, fever, or jaundice. His weight was stable during those 3 months. He had a 7-year history of diabetes mellitus that required insulin injections (aspartic acid insulin [8 IU thrice daily] and insulin glargine [18 IU every night]). He did not have any other significant past medical or family history or allergies.

Physical examinations revealed slight middle abdominal tenderness without rebound tenderness. The primary laboratory examinations revealed the following results: carcinoembryonic antigen (CEA): 1.16 ng/ml (normal: <5 ng/ml), CA-199: 30.02 U/ml (normal: <27 U/ml), WBC: 5.49×10^9/L, RBC: 4.51×10^{12}/L, hemoglobin: 143 g/L, fasting glucose: 7.71 mmol/L, and albumin: 43 g/L. The results of other tests showed no obvious abnormalities

Abdominal contrast-enhanced CT revealed an approximately 7×6 cm solid neoplasm in the body of the pancreas behind the stomach, with no clear border between these two organs. A gastrointestinal stromal tumor or solid pseudopapillary tumor was suspected. The density of the mass was evidently heterogeneous. According to plain CT (Fig. 1), the maximum CT value inside the mass was 54 Hu whereas the minimum was 15 Hu. On the contrast-enhanced CT scan, in the arterial phase (Fig. 2), the maximum value inside the mass was 82 Hu while the minimum was 21 Hu; in the portal vein phase (Fig. 3), the maximum value was 86 Hu while the minimum was 20 Hu; and in the delayed phase (Fig. 4), the maximum value was 69 Hu while the minimum was 31 Hu. Small sporadic calcifications were observed around the envelope of the tumor along with few pelvic ascites. Moreover, the parenchyma of the tumor encircled the splenic

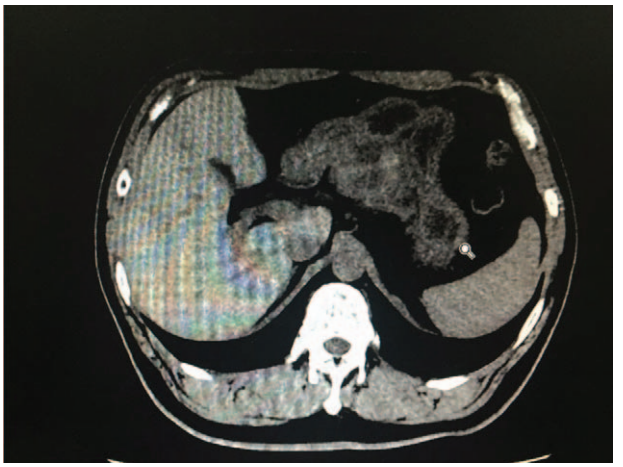

Figure 1. Plain CT scan of the MCN. CT = computed tomography, MCN = mucinous cystic neoplasm.

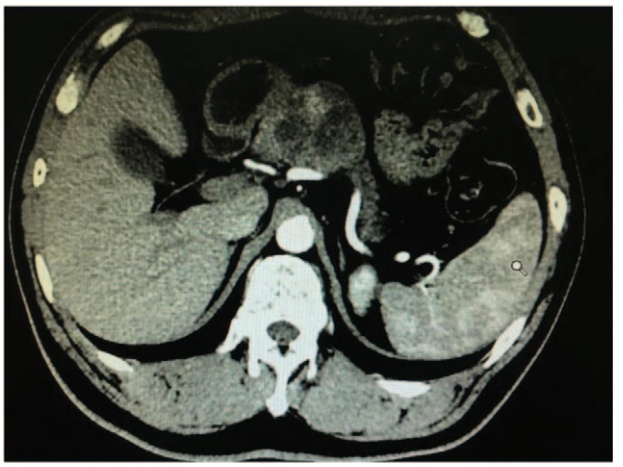

Figure 2. Enhanced CT scan of the MCN (artery phase). CT = computed tomography, MCN = mucinous cystic neoplasm.

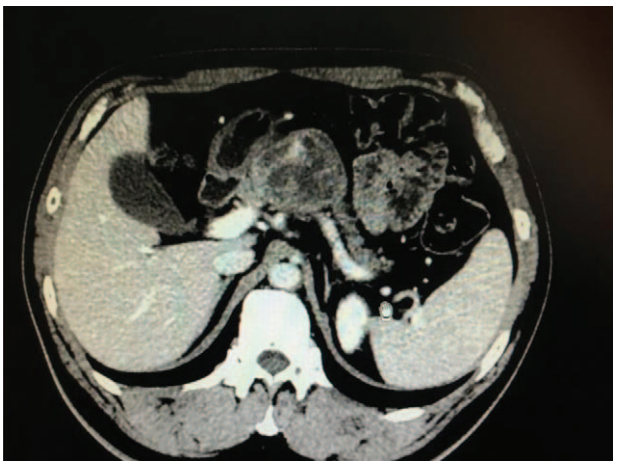

Figure 3. Enhanced CT scan of the MCN (portal vein phase). CT = computed tomography, MCN = mucinous cystic neoplasm.

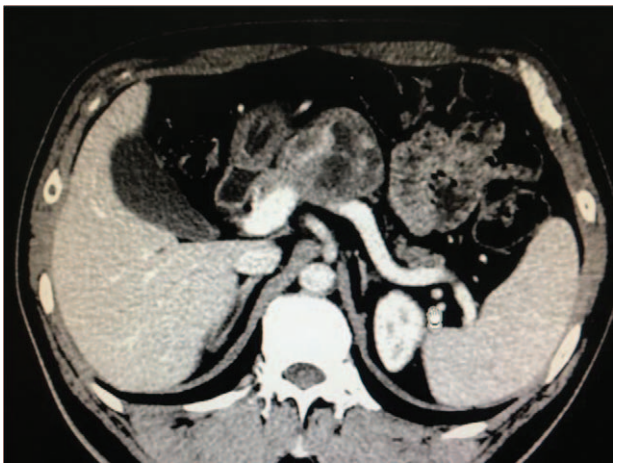

Figure 4. Enhanced CT scan of the MCN (delayed phase). CT = computed tomography, MCN = mucinous cystic neoplasm.

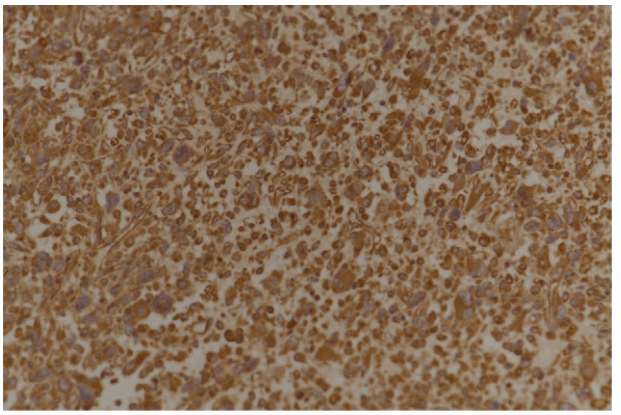

Figure 5. High power view for immunohistochemical results of vimentin.

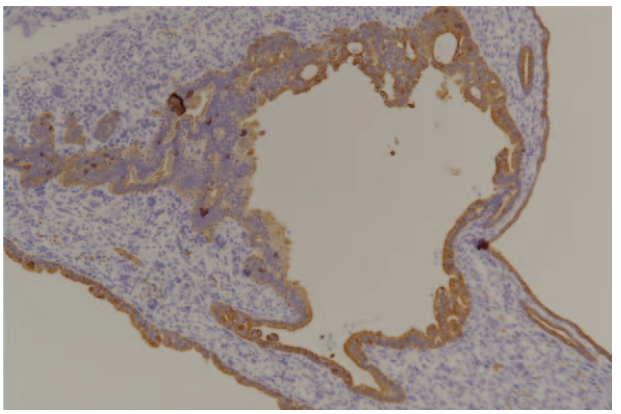

Figure 6. Immunohistochemical results of CK19.

vessels at a high point, along with mild splenomegaly. Moreover, no regional lymphadenopathy or liver metastasis was detected on abdominal CT. However, chest CT revealed a small 1-cm nodule in the middle lobe of the right lung. Endoscopic ultrasound revealed a solid-cystic space-occupying lesion in the body of the pancreas, which was suspected to be a solid pseudopapillary tumor. The results of cardiac ultrasound, pulmonary function, and other preoperative inspections indicated no obvious surgical contraindications.

The preoperative preliminary diagnosis was a pancreatic solid-cystic tumor or a solid pseudopapillary tumor.

The patient underwent open distal pancreatectomy and splenectomy. During surgery, a 6×5 cm solid-cystic encapsulated neoplasm was observed, slightly adherent to the surrounding tissue that occupied the most part of the distal pancreas. The tumor had encircled the junction point of the splenic vein and superior mesenteric vein. The mass was also loosely attached to the posterior gastric wall and could be carefully separated from it. The pancreas was cut off 2 cm away from the tumor margin and en-bloc resection of the mass was performed. Owing to the unsatisfactory separation of the splenic blood vessels and uncertain characteristics of the tumor, we performed splenectomy. The volume of blood loss during the operation was approximately 100 ml, but blood transfusion was not required.

On gross inspection, we observed a pancreatic borderline MCN with an OGCT embedded in a mural nodule of the capsule. The OGCT had a close relationship with the nerve and thick-walled vessels, although the vascular and pancreatic margins were clear. The OGCT showed cystic degeneration with hemorrhage within it. The splenic tissue showed no sign of the tumor.

Immunohistochemical results revealed that the OGCT component was weakly positive for CK (AE1/AE3) and CK8/18 while the MCN was positive for CK (AE1/AE3) and CK8/18. The OGCT was also positive for vimentin (Fig. 5), P53 (+) and Ki67 (MIB-1) (Ki67 index >30%). The MCN was also positive for EMA (+), CK19 (+) (Fig. 6), and BerEp4 (+). While the OGCT was positive for LCA and negative for CA199. However, the MCN was positive for CA199. On the basis of the pathological and immunohistochemical results, the post-operative diagnosis was a borderline pancreatic MCN with a mural nodule containing an OGCT.

The patient showed an uneventful recovery and was discharged from hospital on post-operative day 13. The patient received first-line chemotherapy 1 month after the initial surgery. We intravenously administered single-agent gemcitabine (1.4 g on day 1) and intended to repeat treatment the following week. The dosage was calculated according to his body surface area and latest blood test results. The Plain CT performed during this time (Fig. 7) showed no abnormal signs in the operation region, with pelvic ascites partially resolved, compared to preoperative images. The patient refused to undergo any further postoperative treatment after first-line chemotherapy owing to personal reasons.

3. Follow-up

The patient rechecked the CT scanning of the chest and the abdomen three months after the initial surgery. The operation region showed no signs of recurrence or regional Lymphadenopathy.

Another examination was carried out six months after the initial operation: platelet: 301×10^9/L, postprandial blood glucose: 12.9 mmol/L. Other blood test results showed no significant abnormalities. Tumor marker: CA-199: 20 U/ml. Plain CT scanning of the chest and the abdomen: sporadic small nodules in the right lung, 1.0×0.8 cm for the biggest one (inferior lobe of right lung), no abnormal signs in the operation region. The patient presented no cough, hemoptysis or dyspnea. The

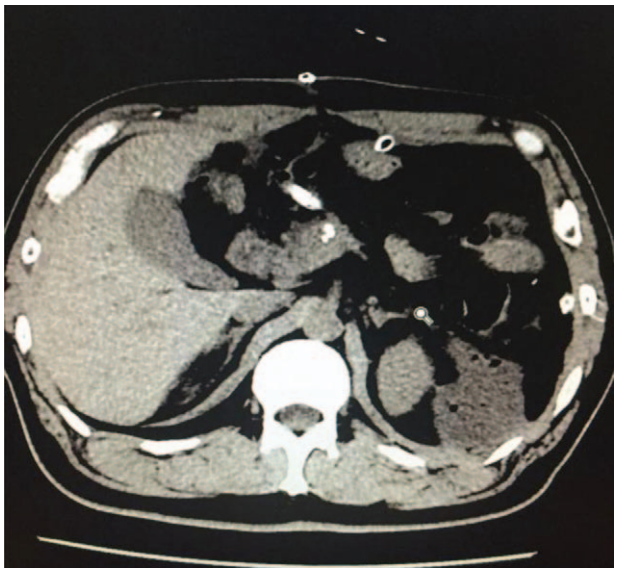

Figure 7. Postoperative CT plain scan. CT = computed tomography.

patient refused needle biopsy for the biggest pulmonary nodules in the inferior lobe.

4. Discussion

About 2%–45% of the population may develop pancreatic cystic neoplasms (PCN) in their whole life screened by CT or magnetic resonance imaging (MRI).[8–11] MCNs of the pancreas account for a relatively small proportion of PCNs. Moreover, the uncertain biological behavior of MCNs is the reason why MCNs are considered borderline tumors. The clinical manifestations of MCNs are nonspecific, such as distending abdominal pain, nausea, vomiting, and weight loss, among other symptoms. Although different imaging modalities such as CT, MRI, and magnetic resonance cholangiopancreatography are available, distinguishing between PCN subtypes is difficult, and identifying mural nodules or solid components of MCNs is also challenging. Therefore, endoscopic ultrasound sometimes is useful to determine the relationship between pancreatic tumors and the adjacent organs (especially the stomach) and to recognize the infiltration depth.

Among laboratory test results, no peripheral blood parameters or biomarkers are capable of accurate recognition of OGCTs or MCNs. The levels of CEA, CA 19-9, amylase, and lipase may be helpful in determining the biological behavior of the tumor.[12]

Regarding the treatment approaches, the recent 2018 European guidelines advocated the use of a conservative approach when the cyst size was <40 mm without risk factors. However, surgery is recommended, irrespective of the size, when mural nodules or systematic symptoms are involved.[13] As a large proportion of MCNs are located in the body/tail of the pancreas, distal pancreatectomy with or without splenectomy is often sufficient.[14]

Although OGCT may have a better prognosis compared with the other two subtypes (pleomorphic and mixed tumors), its disease-free survival is still poor, with controversial results.[15] Moreover, owing to the rarity of the pathological type, the histogenesis and clinical characteristics still remain uncertain. In the current case, the MCN was positive and the OGCT was weakly positive for CK8/18, CK19, AE1, and AE3, which are indicators of epithelial origin. In contrast, the tumor (both components) showed positive immunoreactivity for vimentin and negativity for CD34, which are indicators of mesenchymal origin. These contradictory histological results might indicate the complexity of the neoplastic biological behavior. The tumor also had a Ki67 index of 30%, with positive reactivity for P53, indicative of a relatively poor prognosis.[16]

The point of emphasis here is the consequences and prognosis of the combination tumor. Generally, owing to the uncertain nature of the malignancy, MCNs without risk factors are often regarded as borderline tumors with favorable long disease-free survival if appropriate surgical interventions are performed on time. Nevertheless, OGCTs, as a group of undifferentiated carcinomas, are more likely to show aggressive progression. The latest 2018 European guidelines for PCNs stated mural nodules were an unconditional surgical indication.[13] Moreover, mural nodules are also associated with malignant transformation even though the main body of the mass may appear to be borderline or benign.

The information and analytic results collected from the articles during the 21st century that met our criteria are listed in Table 1. According to our data, there were significant differences in the malignant ratio with or without mural nodules in all studies. Hence, from Table 1, it becomes evident that pancreatic MCNs with mural nodules are more likely to show malignant transformations. In other words, mural nodules, as a prominent risk factor, will increase the malignant ratio of the tumor regardless of the contents inside. These findings partly clarified that MCNs with mural nodules were more likely to show malignant transformation compared with those without nodules. In our particular case, the mural nodule involved an OGCT, an undifferentiated carcinoma. This rare mural nodule in this combination tumor will undoubtedly increase the probability of

Table 1

Malignancy ratio in MCN with or without mural nodules.

First author of study	Year	Follow-up (month)	All patients	With nodule	MA. ratio (n/%)	Without nodule	MA. ratio (n/%)
Kang et al[17]	2017	51.6	55	8	5 (62.5%)	47	4 (8.5%)
Alejandro Garces-Descovich et al[18]	2017	NM	32	4	2 (50.0%)	28	2 (7.1%)
Lauren et al[1]	2016	27	289	71	22 (30.9%)	218	30 (13.7%)
Park et al[19]	2014	37.9	65	6	3 (50.0%)	59	2 (3.4%)
Zhong et al[20]	2012	NM	57	22	5 (22.7%)	35	1 (2.9%)
Yamao et al[21]	2011	120	156	42	14 (33.3%)	114	13 (11.4%)
Crippa et al[22]	2008	57	163	24	18 (75.0%)	139	10 (7.2%)
Procacci et al[23]	2001	NM	52	9	5 (55.6%)	43	11 (25.6%)

MA = malignant, MCN = mucinous cystic neoplasm, NM = not mentioned.

malignant biological behavior, thereby having a negative effect on the prognosis, which will require close long-term follow-up and strict monitoring of the patient.

5. Conclusion

Compared to pancreatic adenocarcinoma or other invasive tumors, MCNs of the pancreas are borderline neoplasms with a relatively favorable prognosis. However, malignant transformation occurs in pancreatic MCNs, including dysplasia and carcinoma. Various risk factors and potential characteristics had been previously described, including cyst size≥4 cm, septations, mural nodules, and tumor location in the pancreas. Considering the gender ratio (female:male = 20:1) of this tumor type, this uncommon case of a pancreatic MCN with a mural nodule containing OGCT is important as this was observed in a male patient. We also focused on the prognostic impact of the mural nodule, in which a relatively much more invasive tumor occurred. Finally, owing to the rarity of this combination tumor among PCNs and limited follow-up time for this case, more studies are needed to determine the long-term prognosis.

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Supervision: WenYue Wang.
Validation: Tao Tang.
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