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Invasive Ductal Carcinoma Arising in Mucinous Cystic Neoplasm of Pancreas: A Case Report

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Conflict of interest: None declared

Patient: Female, 40
Final Diagnosis: Invasive ductal carcinoma arising in mucinous cystic neoplasm of pancreas
Symptoms: None
Medication: —
Clinical Procedure: Surgical resection
Specialty: Oncology

Objective: Rare co-existance of disease or pathology

Background: Mucinous cystic neoplasm (MCN) of the pancreas is a rare mucin-producing cystic neoplasm that has a characteristic histological feature referred to as ovarian-type stroma (OS) underlying the epithelium. Pancreatic ductal carcinoma arises from MCN as a precursor lesion, but data on progression pathways are limited.

Case Report: A 40-year-old female was referred to our hospital for further investigation of a pancreatic cyst. Further examination showed a 7.0 cm multilocular cyst in the pancreatic tail and a solid mass in the thick septum of the cystic tumor. Distal pancreatectomy and splenectomy were performed. Histological examination revealed a moderately differentiated invasive ductal carcinoma (IDC) with a diameter of 0.5 cm in the thick septum of the cystic lesion and a cyst wall composed of epithelium with low-grade to severe dysplasia. The epithelium covered an OS. Pathological diagnosis was IDC arising in MCN of the pancreas. Immunohistochemical examination showed that MUC1 expression was negative in MCN but positive in IDC. *KRAS* mutation was observed in both MCN and IDC regions.

Conclusions: We present a rare case of moderately differentiated pancreatic IDC arising in MCN. To elucidate the underlying progression pathway, we explored the correlation between *KRAS* mutation and MUC expression as a clinicopathological parameter.

MeSH Keywords: Carcinoma, Pancreatic Ductal • Cystadenoma, Mucinous • Genes, ras • Mucin-1 • Pancreas

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Background

Compagno and Oertel [1] proposed to separate cystic, mucin-producing pancreatic neoplasm from serous cystic neoplasm of the pancreas in 1978. The World Health Organization (WHO) further classified mucin-producing cystic tumors of the pancreas into 2 distinct entities: mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN) [2]. The former is a rare, multicystic pancreatic tumor characterized by ovarian-type stroma (OS). It occurs almost exclusively in the body or tail of the pancreas in middle-aged women. Yamao et al. [3] reported that MCN features a favorable prognosis if diagnosed in the presence of OS. Noninvasive MCN is curative with an excellent survival rate achieved by complete surgical resection; however, for MCN with advanced invasive carcinoma of the pancreas, the 5-year disease-specific survival rate is 20% to 60% for patients [3–7]. To prevent progression to malignancy, all MCNs should be resected at a time when the lesion is small and mural nodules are absent. We herein present a rare case of a moderately differentiated invasive ductal carcinoma (IDC) arising in an MCN of the pancreas. Furthermore, we examined the differential expression of Mucin (MUC) and *KRAS* mutation in the MCN and IDC to investigate the pathway of malignant transformation in pancreatic cystic neoplasm.

Case Report

A 40-year-old female patient was found to have a 7.0 cm tumor in the pancreatic tail from ultrasound examination. The patient's serum cancer antigen (CA) 19-9 level was within the normal range (<37 U/mL). Computed tomography (CT) demonstrated a 7.4×6.2×7.6-cm complex cystic mass in the pancreatic tail with irregular, enhancing internal septations and nodular foci of mural enhancement (Figure 1A, 1B). T2-wieghted magnetic resonance imaging revealed that the cystic tumor was 6.8 cm in diameter and a thickening septum (Figure 1C, 1D). There were no pancreatic or biliary ductal dilatation and no

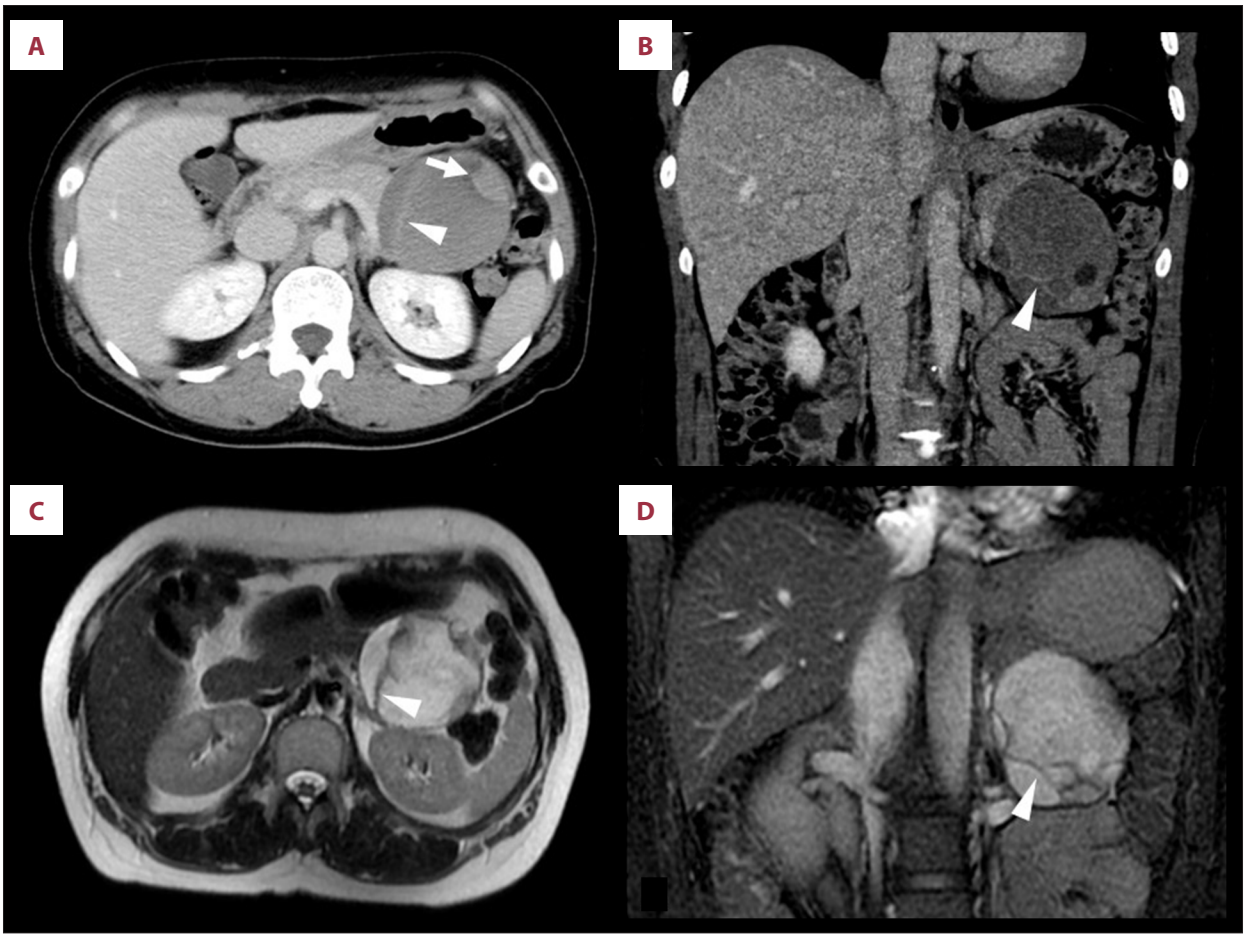

Figure 1. Enhanced computed tomography (CT) and T2-weighted magnetic resonance imaging (MRI) images. CT showed a multilocular cystic lesion in the pancreatic tail with irregular, enhancing internal septations (white arrowheads) and nodular foci (white arrow) of mural enhancement (**A, B**). MRI showed the cystic tumor with a thickening septum seen (white arrowheads) on T2-weighted imaging (**C, D**).

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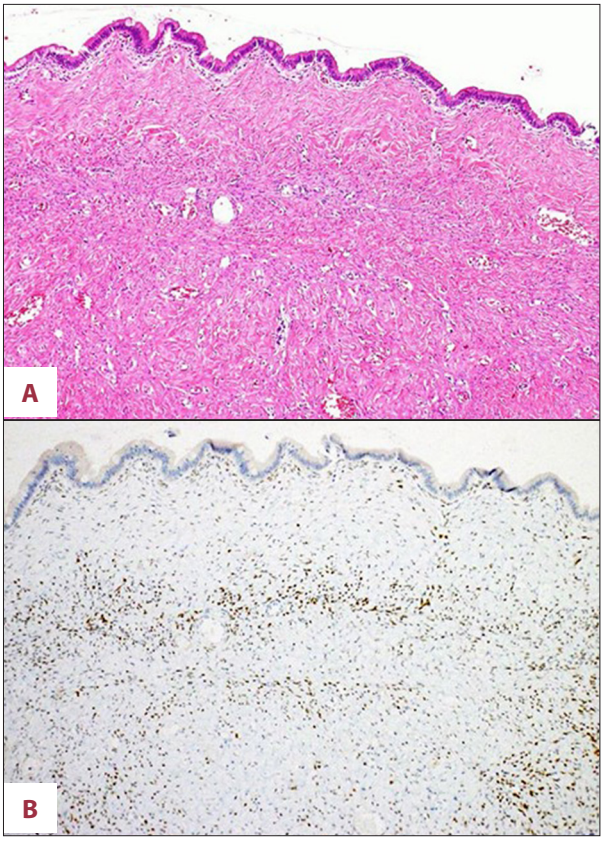

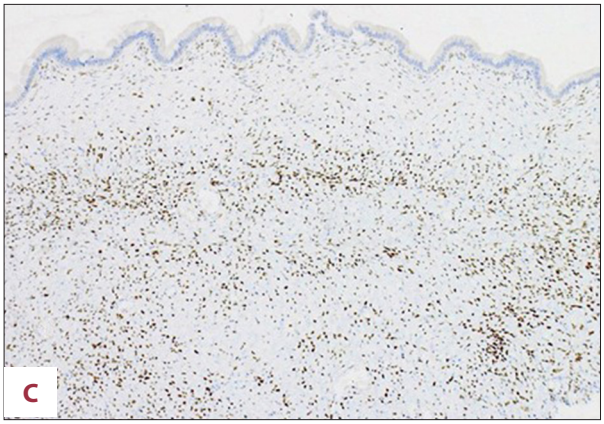

Figure 2. Microscopic and immunohistochemical analysis of MCN. The cyst wall was lined with benign mucinous columnar epithelium underlying OS, (**A**) Hematoxylin and eosin, 100×). This stroma was immunoreactive for estrogen and progesterone receptors (**B**) estrogen receptor staining, 100×; (**C**) progesterone receptor staining, 100×. MCN – mucinous cystic neoplasm; OS – ovarian-type stroma.

connection to the pancreatic ductal system. In addition, fluorodeoxyglucose positron emission tomography CT showed normal uptake in part of the cystic tumor. As we were concerned about the malignant potential of the lesion, we performed distal pancreatectomy and splenectomy. Macroscopically, we observed a multiloculated 7.0 cm cystic tumor filled with mucinous fluid and a fibrotic wall but no solid mass lesion. Microscopically, the cyst wall was lined by cuboidal columnar epithelial cells with low-grade to high-grade dysplasia underlying OS (Figure 2A). Immunohistochemical analysis showed that both estrogen receptor and progesterone receptor were partially positive in the nucleus of the OS (Figure 2B, 2C). In the superficial layer of the cyst wall in the OS, a moderately differentiated IDC measuring up to 0.5 cm was identified. (Figure 3A). Furthermore, transitional findings from mucinous cystadenoma to IDC were observed (Figure 3B). Additional immunohistochemical analysis revealed that only MUC1 was expressed in the region of the IDC; MUC1 was not expressed in the region of the MCN, where only MUC5AC expression was observed (Figure 3C, 3D; Table 1). The 7 resected lymph nodes were negative for carcinoma, and the pancreatic margin was negative for tumor. The pathological stage was stage IA (T1a, N0, M0) according to the classifications of the American Joint Committee on Cancer (AJCC) [8]. Contrary to the results of MUC immunostaining, a mutation of *KRAS* codon 12 (G12D) was observed in both the MCN and the IDC regions (Table 1).

Considering the patient's young age, the patient postoperatively received oral administration of S-1 (an oral 5-fluorouracil prodrug) twice daily at a dose of 100 mg/day according to body surface areas for 28 consecutive days followed by a 14 day rest, as an adjuvant chemotherapy; however, she could not continue the chemotherapy for more than 2 courses due to adverse drug reactions such as liver dysfunction and increased bilirubin level. Thereafter, she received close follow-up with no further treatment. There was no recurrence by the 37-month follow-up.

Discussion

Though previous reports have acknowledged OS as usually present in but not required for the diagnosis of MCN [9], the Consensus Conference of the International Association of Pancreatology in Sendai (Japan) established that the histological presence of unique OS was mandatory to diagnose MCN, as OS was never found in other pancreatic neoplasms in 2004 [10]. IPMN has often been confused with MCN which partly accounts for this shift in diagnosis criteria, as the 2 conditions feature similarities in their cystic appearance and mucin-producing epithelium [11]. Further confounding diagnosis, MCN-like lesions without OS have been observed to cause similar clinicopathological features to those of MCNs with OS [12]. To avoid such confusion, Yamao et al. [3] strictly defined MCN by the presence of OS.

According to the Armed Forces Institute of Pathology classifications published in 2007, MCN is divided into 4 categories: MCN with low-grade dysplasia, MCN with moderate dysplasia, MCN with high-grade dysplasia (carcinoma *in situ*), and invasive

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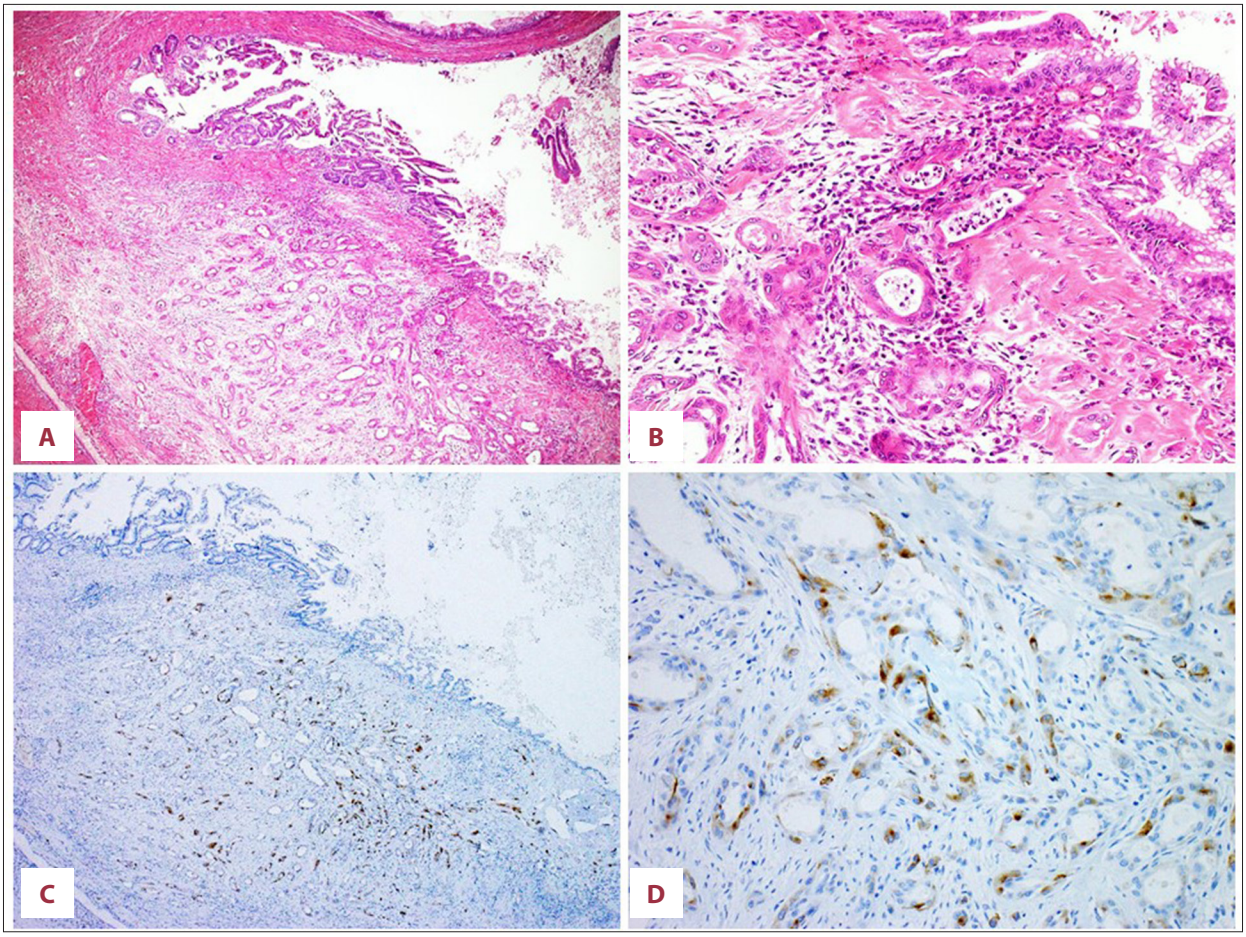

Figure 3. Microscopic and immunohistochemical analyses of the transitional region from MCN to IDC. IDC (moderately differentiated type) was identified in the superficial layer of the cyst wall in the OS, (**A**) hematoxylin and eosin, 40×. Transitional findings from mucinous cystadenoma to IDC were observed: (**B**) hematoxylin and eosin, 200×. Immunohistochemical analysis showed MUC1 expression in the region of IDC, whereas MUC1 was not expressed in the region of MCN cyst wall lined with mucinous columnar epithelium underlying OS (MUC1 staining, **C** 40×, **D** 200×). MCN – mucinous cystic neoplasm; IDC – invasive ductal carcinoma; OS – ovarian-type stroma.

Table 1. Findings of MUC immunostaining and *KRAS* mutation.

	Dysplasia of MCN	IDC
MUC1	Negative	Positive
MUC5AC	Positive	Negative
KRAS codon 12	G12D	G12D
KRAS codon 13	WT	WT

MCN – mucinous cystic neoplasm; IDC – invasive ductal carcinoma. WT – wild type.

mucinous cystadenocarcinoma [13]. According to the pathological classification of the seventh edition of the General Rules for the Study of Pancreatic Cancer published in 2016, the Japan Pancreatic Society classified MCN into cystadenoma, noninvasive cystadenocarcinoma, and invasive adenocarcinoma [14]. Noninvasive MCN is categorized as MCN low-grade, intermediate-grade, or high-grade dysplasia. If there is a component of invasive carcinoma, the lesions are designated as MCN with an associated invasive carcinoma.

Zamboni G et al. [11] reported that MCNs associated with pancreatic invasive adenocarcinoma follow the same pathways of local spread as invasive ductal adenocarcinoma. In our case, a moderately differentiated IDC measuring up to 0.5 cm in size was identified in the superficial layer of the cyst wall in the OS. Furthermore, transitional findings from mucinous cystadenoma to IDC were observed. The pancreatic IDC of less than 0.5 cm developing in the MCN like in this case is extremely rare. According to the AJCC classification, the significance and characteristics of T1a (≤0.5 cm) and T1b (>0.5 and <1.0 cm) carcinomas arising in the MCN is unclear. Hui et al. [6] reported that T1a and T1b carcinomas developing in association with

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an MCN have an excellent prognosis, like those of MCN with low-grade dysplasia or MCN with high-grade dysplasia. They also mentioned that careful histologic examination of the entire tumor is critical to identifying microscopic invasion (T1a and T1b carcinoma) if no invasive carcinoma is grossly identified. Despite their findings of complete sampling of the tumor, Hui et al. concluded that rather than aggressive systemic therapy, close follow-up might be a better approach to manage patients with T1a and T1b carcinoma arising in an MCN.

On the other hand, pancreatic IDC is an extremely lethal disease, which is characterized by its propensity to infiltrate adjacent tissues and to metastasize even at early stages [15–17]. Furthermore, IDC remains a disease of high mortality despite the availability of diagnostic and therapeutic techniques [18–21]. *KRAS* is well known to be a significant early driver in the carcinogenesis of IDC of pancreas [22,23]. Sinn et al. [24] reported that *KRAS* mutations in codon 12 or 13 were associated with worse prognosis of pancreatic ductal adenocarcinoma. *KRAS* mutations have also been identified in MCN, although the frequency of reported mutations has been variable [25–27]. Recently, Conner et al. [28] reported that *KRAS* mutations were present in all high-grade dysplasia; similar to what is found for conventional ductal adenocarcinoma, and this report suggested that the gene is significant to the pathogenesis of pancreatic adenocarcinomas arising from MCN. Among low-grade dysplasia lesions, however, *KRAS* mutations are reportedly less frequent. In our present case, the same *KRAS* mutation was observed in the IDC and the MCN regions, suggesting the possibility that MCN cells featured a higher malignant potential.

MUC1, a high-molecular-weight transmembrane mucin, plays crucial roles in carcinogenesis and tumor invasion in pancreatic neoplasms. These are overexpressed in many carcinomas, and high expression of these molecules is a risk factor associated with poor prognosis [21,29–32]. In the present case, immunohistochemical analysis revealed MUC1 expression in the transitional region from MCN to IDC; its expression was not observed in the MCN region. On the other hand, MUC5AC expression in MCN region was absent in IDC region.

In this report, we examined *KRAS* mutation and its correlation with MUC expression as a clinicopathological parameter to elucidate the mechanism of tumor malignant transformation. Fujikura et al. [33] reported a positive correlation between *KRAS* mutation and MUC expression, especially the expressions of MUC1, MUC2, and MUC5AC. Molecular biological roles of MUC5AC in carcinogenesis are still unclear; however, it was suggested that MCN cells with *KRAS* mutation acquired MUC1 expression and lost MUC5AC expression in the course of malignant transformation. To the best of our knowledge, this is the first report of clear transitional findings from MCN to IDC and malignant transformation demonstrated by the investigation of MUC expression and *KRAS* mutation.

Conclusions

In summary, we encountered a rare case of a moderately differentiated IDC arising in MCN of the pancreas. Of course, with an increase in cases of MCN of pancreas, it cannot be denied that these results could change to some extent and new findings may arise. However, our findings suggest that MUC1 expression and *KRAS* mutation may contribute to an underlying mechanism of malignant transformation of pancreatic cystic neoplasm. The characteristics of MCN are still poorly understood, requiring further investigations to clarify the biological malignancy of MCN.

Department and Institution where work was done

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Conflicts of interest

None.

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