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【 CASE REPORT 】

Oncocytic Type Intraductal Papillary Mucinous Neoplasm of the Pancreas with Unusually Low Mucin Production Mimicking Intraductal Tubulopapillary Neoplasm: A Report of a Case Diagnosed by a Preoperative Endoscopic Biopsy

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Abstract:

We herein report the case of a 78-year-old woman with an intraductal tumor with scant mucin production in a moderately dilated main pancreatic duct that resembled an intraductal tubulopapillary neoplasm (ITPN) on imaging. An endoscopic transpapillary forceps biopsy enabled an accurate preoperative diagnosis of the tumor as an oncocytic type intraductal papillary mucinous neoplasm (IPMN) of the pancreas microscopically showing papillary growth consisting of oncocytic cells with a typical mucin expression profile, although with few intraepithelial lumina containing mucin. This is the first case of an oncocytic type IPMN mimicking an ITPN that was able to be diagnosed preoperatively.

Key words: oncocytic type, IPMNs, IOPNs, preoperative diagnosis, endoscopic biopsy

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Introduction

Clinically, the majority of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas show cystic dilation of the branch ducts and/or dilation of the main pancreatic duct (MPD), particularly marked MPD ectasia in the main duct type, with or without mural nodules (1-3). The imaging features of IPMNs are derived from the nature of neoplastic cells producing copious mucin. However, unusual IPMNs without typical imaging findings have been reported (4-6), and are difficult to diagnose, even as IPMN itself, by imaging alone.

In 2010, the World Health Organization (WHO) classified IPMNs based on histomorphologic features into four distinct epithelial types: gastric, intestinal, pancreatobiliary, and oncocytic (3). Among these subtypes, the oncocytic type has proven to be the least common variant (<5%) according to the latest systematic review (7). Recently, oncocytic type IPMNs (O-IPMNs), albeit rare, have been noted to be confusing tumors in the differential diagnosis of pancreatic neoplasms due to their atypical radiologic findings (6, 8).

We herein report an unusual case of a main duct O-IPMN of the pancreas with far less mucin production than is commonly seen mimicking an intraductal tubulopapillary neoplasm (ITPN). This lesion was preoperatively confirmed via biopsy specimens.

Case Report

A 78-year-old Japanese woman was referred to our hospital for treatment of diverticulitis of the colon. Abdominal contrast-enhanced computed tomography (CT) showed inflammation of the wall of the descending colon and inciden-

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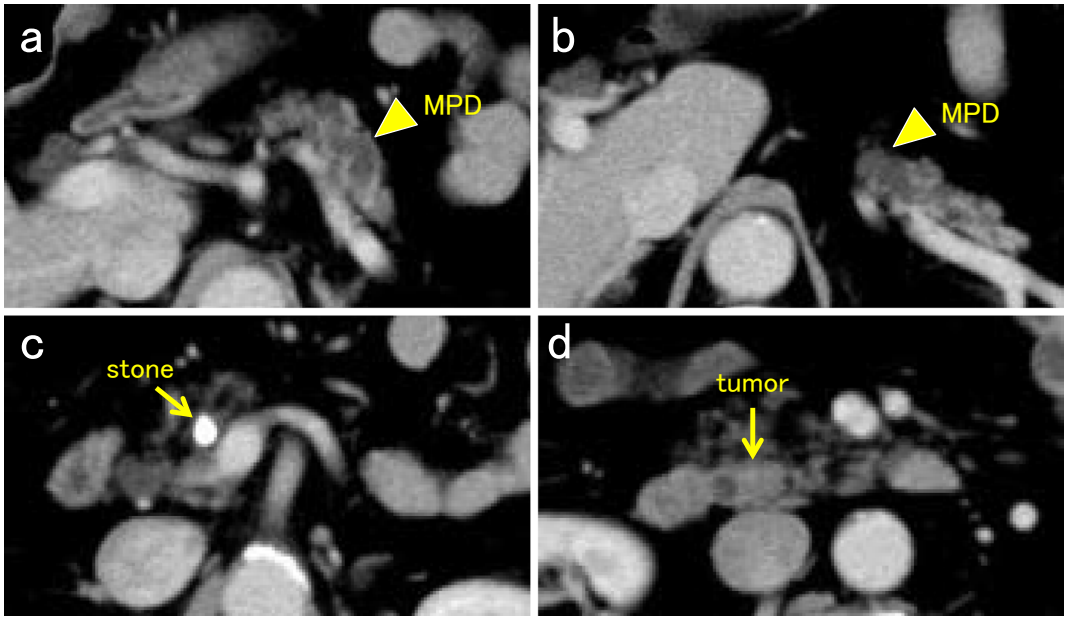

Figure 1. **Abdominal contrast-enhanced CT shows severe atrophy of the pancreas with moderate dilation of the MPD (arrowhead) and a stone (arrow) in the MPD (a, b, and c). A slightly enhanced tumor (arrow) in the head of the pancreas that was missed at the time of diagnosis can be seen (d). MPD: main pancreatic duct**

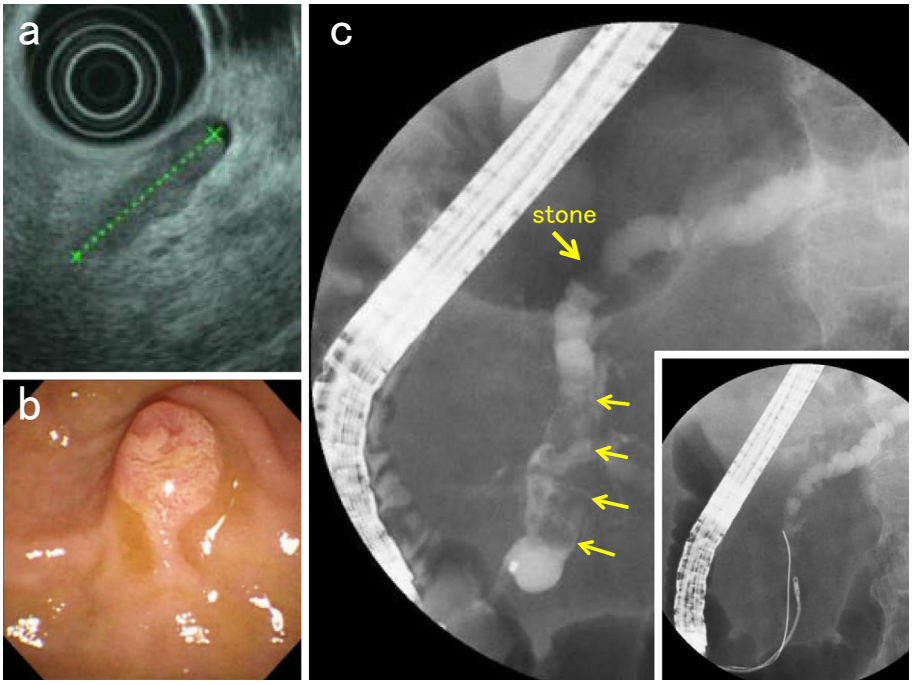

Figure 2. **EUS imaging shows a homogeneous hypoechoic mass, 28 mm in length, that fills the MPD of the head of the pancreas. However, no invasion to the adjacent pancreatic parenchyma is evident (a). The appearance of the papilla of Vater is normal, without a dilated ampullary orifice or mucin extrusion (b). ERCP shows a tumor (4 arrows) occupying the cephalic MPD and a stone (arrow) as a filling defect in the dilated MPD (c). During ERCP, a transpapillary forceps biopsy under guidewire assistance was successfully performed (c, inset). EUS: endoscopic ultrasonography, MPD: main pancreatic duct, ERCP: endoscopic retrograde cholangiopancreatography**

tally showed severe atrophy of the pancreas with moderate dilation of the MPD and a stone in the MPD (Fig. 1a-c). However, there was no evidence of a clearly enhanced tumor in the head of the pancreas at that time (Fig. 1d). Magnetic resonance cholangiopancreatography showed a filling defect in the MPD of the head of the pancreas. On endo-

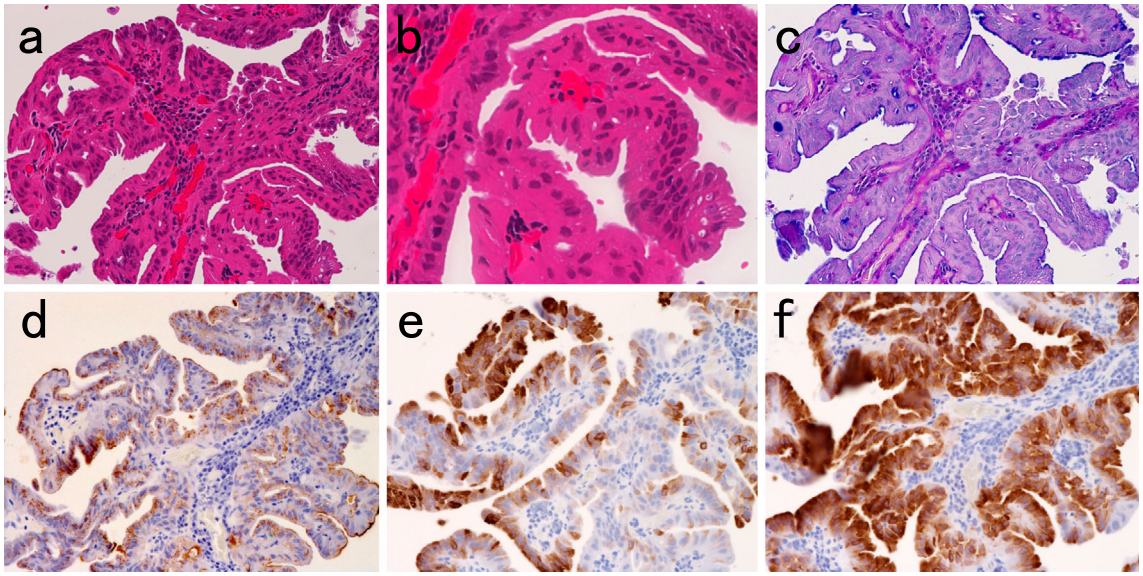

Figure 3. **A microscopic examination of a biopsy specimen from the tumor shows a papillary growth pattern. The tumor consists of large eosinophilic cells, so-called oncocytic cells, indicating oncocytic type IPMN of the pancreas. Mucin-containing intraepithelial lumina are not prominent (a and b), and few are lumina stained with PAS-AB (c). The tumor is immunohistochemically positive for MUC1 and MUC5AC, and strongly positive for MUC6 (d, e, and f). IPMN: intraductal papillary mucinous neoplasm, PAS-AB: periodic acid Schiff-Alcian blue**

scopic ultrasonography (EUS), a homogeneous hypoechoic mass 28 mm in length filled the cephalic MPD without any findings of invasion to the adjacent pancreatic parenchyma (Fig. 2a). The maximum caliber of the MPD scaled by EUS was 7 mm. Neither a dilated ampullary orifice nor any mucin outflow from the papilla was noted (Fig. 2b). These results were suggestive of an intraductal neoplasm of the pancreas without mucin hypersecretion, leading to a definitive diagnosis by a histologic examination.

During endoscopic retrograde cholangiopancreatography (ERCP), a transpapillary forceps biopsy was successfully performed (Fig. 2c). One of three specimens obtained showed a microscopic papillary growth pattern that consisted of large eosinophilic cells, so-called oncocytic cells, with moderate atypia of the nuclei (Fig. 3a and b), although intraepithelial mucin-containing lumina characteristic of O-IPMNs (2) were not prominent. There were indeed few intraepithelial lumina reactive on periodic acid Schiff-Alcian blue (PAS-AB) staining (Fig. 3c), but the immunohistochemical findings of mucin core protein expression of tumor cells showed MUC1(+), MUC2(-), MUC5AC(+), and MUC6 (++), findings that were consistent with an oncocytic phenotype (Fig. 3d-f) (9). ITPN, which inherently never expresses MUC5AC, was excluded. Thus, main duct O-IPMN was preoperatively confirmed via biopsy specimens. Distant metastases were not detected by sequential imaging modalities. The patient's laboratory data, including carbohydrate antigen 19-9, showed no abnormal findings before surgery.

Duodenum-preserving pancreatic head resection (10) was performed, since tumor invasion to the pancreatic parenchyma was not evident on imaging, particularly on EUS. Informed consent was obtained from the patient regarding the limited operation. A histopathological examination of the resected tissue showed a solid tumor that measured 25×8×6 mm occupying the cephalic MPD without visible mucin and complete removal as a noninvasive tumor (Fig. 4a and b). A stone (6 mm in diameter) was found in the MPD. Microscopically, the tumor showed complex papillary structures composed of oncocytic cells with intermediate- to high-grade dysplasia, and intraepithelial lumina positive for PAS-AB were seen infrequently throughout the entire tumor (Fig. 4c-e). The mucin expression profile of the tumor showed the oncocytic immunophenotype (Fig. 5), corresponding to the results of the biopsy specimen examinations. The ultimate diagnosis was noninvasive main duct O-IPMN of the pancreas. The patient's postoperative course was uneventful, and she is now in good health without any digestive symptoms or evidence of tumor recurrence at three years after the operation.

Discussion

O-IPMN is identical to intraductal oncocytic papillary neoplasm (IOPN), which Adsay et al. originally described in 1996 (11), and in 2010, Liszka et al. first reviewed 28 cases of pancreatic IOPN (12). Based on the latest systematic review of IPMN in 2015 (7) and 2 more recent reports on O-IPMN (13, 14), the ratio of main duct type and the median size of the cystic tumors range from 37.9% to 72.2% and from 46.35 to 56.9 mm, respectively. These data indicate that O-IPMNs grow within the MPD in about half of cases and usually show relatively large cystic masses. In addition,

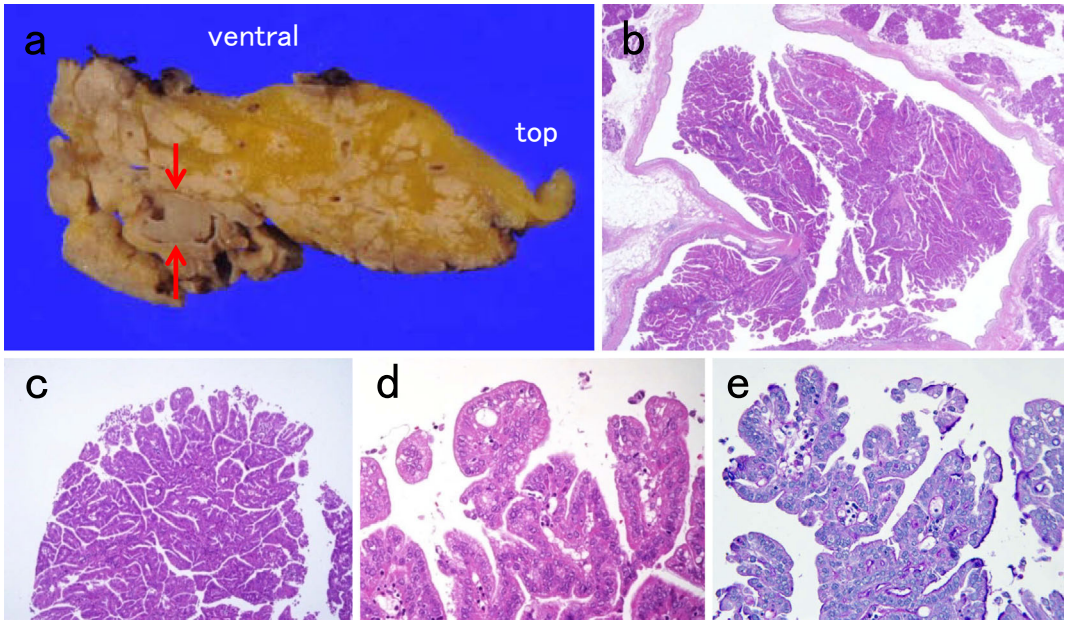

Figure 4. **The cut surface of the resected tissue is shown. A grayish-brown solid tumor (red arrows) fills the MPD (a). A histopathological examination shows a noninvasive tumor originating from the intraductal epithelium (b). Microscopically, the tumor shows complex papillary structures with intermediate- to high-grade dysplasia and is composed of oncocytic cells (c and d). Intraepithelial mucin-containing lumina positive for PAS-AB are infrequently seen throughout the entire tumor (e). MPD: main pancreatic duct, PAS-AB: periodic acid Schiff-Alcian blue**

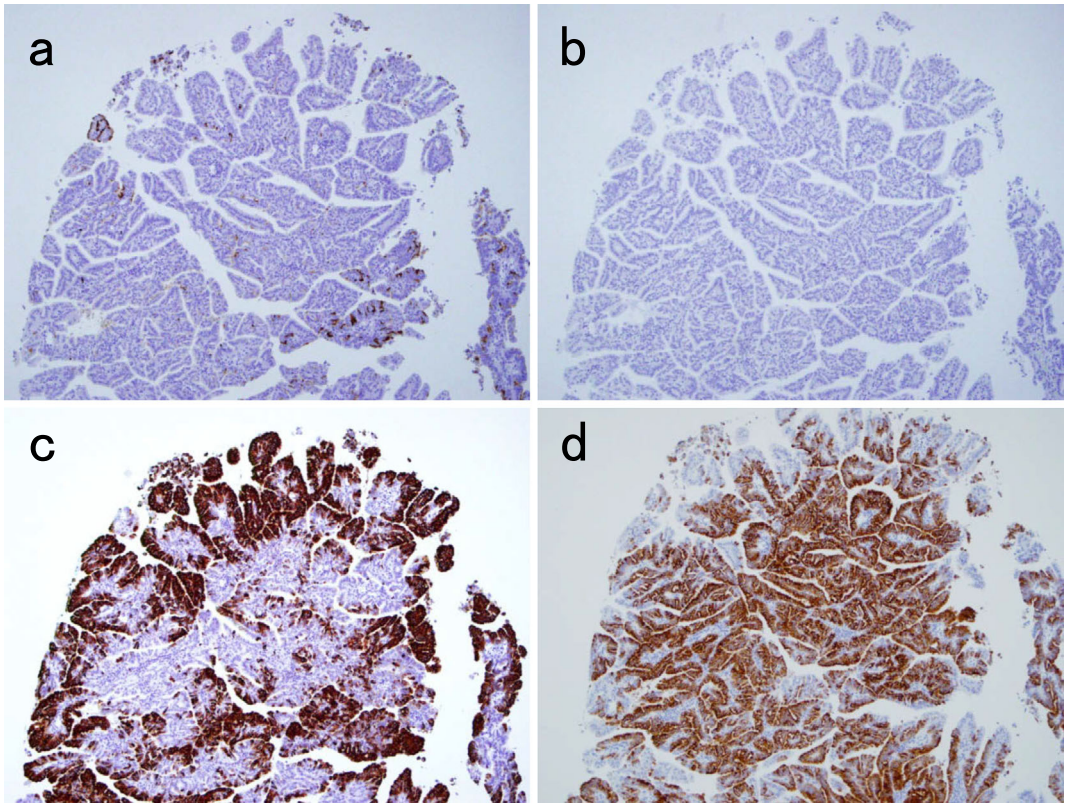

Figure 5. **The mucin expression of the resected tissue by immunohistochemistry is shown. The tumor is focally positive for MUC1 (a), negative for MUC2 (b), and positive for MUC5AC (c) and MUC6 (d).**

D'Onofrio et al. found in their series of 16 O-IPMNs that all 10 main duct type lesions presented with MPD dilation of ≧10 mm on imaging studies (14). The present case, however, despite being main duct type, had neither cystic le-

sions nor excessive MPD dilation, and it seemed to be an unusual example of the oncocytic variant. O-IPMNs are cytologically characterized by oncocytic cells showing abundant eosinophilic cytoplasm due to rich mitochondria, and they are also architecturally characterized by a cribriform pattern with mucin-containing intraepithelial lumina along with very complex papillary structures (2, 15). In the present case, very low mucin productivity of the tumor, supported by the scarcity of intraepithelial lumina stained with PAS-AB, was likely to be the reason why the tumor did not appear as typical main duct type IPMN on imaging.

The lack of imaging features of IPMN in this case required a cytohistologic examination for the differential diagnosis of a main duct IPMN without mucin hypersecretion from an ITPN, which is also categorized as a rare new entity of intraductal neoplasm of the pancreas in the 2010 WHO system (3). While information is limited (16, 17), ITPNs clinically show solid growth in the MPD and are histologically characterized by a tubulopapillary architecture with scant cytoplasmic mucin. The tumor in the present case, which had scant mucin production and moderate MPD dilation, resembled an ITPN on imaging. However, we were able to make an accurate diagnosis of O-IPMN preoperatively based on the histologic evaluation of biopsy specimens. To our knowledge, no previous reports have described the successful preoperative diagnosis of O-IPMN mimicking ITPN.

Reid et al. recently have urged clinicians to keep in mind that O-IPMNs are often radiologically complex cystic masses with a more solid appearance than other IPMN subtypes, which can lead to a misdiagnosis as cystadenocarcinoma or pancreatic ductal adenocarcinoma (PDAC) with cystic changes (8). One explanation for this potential confusion is that O-IPMNs are typically less mucinous than other IPMNs. The authors also documented the usefulness of cytologic assessment via an EUS-guided fine-needle aspiration biopsy for the differential diagnosis of O-IPMNs from other IPMN subtypes or PDACs, although the procedure for cystic masses is still being debated.

Recent advances in our understanding of IPMN have revealed the prognostic significance of the histologic subtypes (13, 18-20), wherein the O-IPMN has a better outcome than expected, despite its cytohistologic atypia. Furukawa et al. reported the association between O-IPMN and a minimally invasive phenotype (18). In the series reported by Marchegiani et al., the survival outcomes of patients with invasive tumors were extremely favorable, even after a second resection for recurrence (13). For the present patient, although the tumor was noninvasive, careful long-term follow-up is necessary, since O-IPMNs appear to carry a high risk for late recurrence of multifocal disease in the remnant pancreas (13, 21, 22).

Genetically, IPMNs are reported to often harbor activating mutations in *KRAS* and/or *GNAS* (1, 23). In particular, *GNAS* mutations are specific for IPMN among pancreatic neoplasms. However, in most O-IPMNs, neither of the genes is mutated (23, 24), suggesting that O-IPMN has a molecular pathogenesis different from other IPMN subtypes and is thus recognized as a distinct entity.

In conclusion, it should be noted that O-IPMN can mimic other types of pancreatic neoplasms, including ITPN, as shown in the present case. For a better understanding of the clinicopathologic characteristics of O-IPMN of the pancreas, a rare but unique tumor, a larger number of cases, including unusual individual cases, need to be accumulated and evaluated.

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

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