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

Yukinari Yoshida¹, Takao Endo¹, Eiichi Tanaka², Takefumi Kikuchi¹, Kimishige Akino¹, Hiroaki Mita¹, Yasuyo Adachi¹, Masahiro Nakamura¹, Yasushi Adachi¹, Yoshifumi Ishii³, Joe Matsumoto², Satoshi Hirano², Takeo Nitta², Tomoko Mitsuhashi⁴ and Yasuo Kato¹

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-
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

Initially 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-
scopric 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,
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 oncocyty variant. O-IPMNs are cyto-
tologically characterized by oncocyty cells showing abun-
dant eosinophilic cytoplasm due to rich mitochondria, and
they are also architecturally characterized by a cribiform
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 ap-
pear as typical main duct type IPMN on imaging.

The lack of imaging features of IPMN in this case re-
quired a cytohistologic examination for the differential diag-
nosis of a main duct IPMN without mucin hypersecretion
from an ITPN, which is also categorized as a rare new en-
tity 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 his-
tologically 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 preopera-
tively based on the histologic evaluation of biopsy speci-
mens. 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 sub-
types, which can lead to a misdiagnosis as cystadenocarci-
noma or pancreatic ductal adenocarcinoma (PDAC) with
cystic changes (8). One explanation for this potential confu-
sion is that O-IPMNs are typically less mucinous than other
IPMNs. The authors also documented the usefulness of cy-
tologic 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 re-
vealed the prognostic significance of the histologic sub-
types (13, 18-20), wherein the O-IPMN has a better out-
come than expected, despite its cytohistologic atypia. Fu-
rukawa 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 sec-
ond resection for recurrence (13). For the present patient, al-
though 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 pan-
creas (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 molecu-
lar 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 evalu-
ated.

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

References

1. Tanaka M. Thirty years of experience with intraductal papillary
mucinous neoplasm of the pancreas: from discovery to interna-
tional consensus. Digestion 90: 265-272, 2014.
2. Adsay NV, Daniel MD. Longnecker DS, et al. Pancreatic tumors
with cystic dilatation of the ducts: intraductal papillary neoplasms
and intraductal oncocytic papillary neoplasms. Semin Diag Pathol
17: 16-30, 2000.
3. Adsay NV, Fukushima N, Furukawa T, et al. Intraductal neo-
plasms of the pancreas. In: WHO Classification of Tumors of the
Digestive System. Boston FT, Carneiro F, Hruban RH, Theise ND,
Eds. IARC Press, Lyon, France, 2010: 304-313.
4. Oku T, Maeda M, Wada Y, et al. Intraductal oncocytic papillary
neoplasm having clinical characteristics of mucinous cystic neo-
plasm and a benign histology. JOP 8: 206-213, 2007.
5. Fischler MA, Donati O, Heinrich S, et al. Intraductal oncocytic
papillary neoplasms of the pancreas: a radio-pathological case
study. JOP 11: 49-54, 2010.
6. Kallen ME, Naini B. Intraductal oncocytic papillary neoplasms
of the pancreas. Arch Pathol Lab Med 140: 992-996, 2016.
7. Koh YK, Zheng HL, Chok AY, et al. Systematic review and meta-
analysis of the spectrum and outcomes of different histologic sub-
types of noninvasive and invasive intraductal papillary mucinous
neoplasms. Surgery 157: 496-509, 2015.
8. Reid MD, Stallworth CR, Lewis MM, et al. Cytopathologic diag-
nosis of oncocytic type intraductal papillary mucinous neoplasm:
Criteria and clinical implications of accurate diagnosis. Cancer
Cytopathol 124: 122-134, 2016.
9. Furukawa T, Klöppel G, Adsay NV, et al. Classification of types
of intraductal papillary-mucinous neoplasm of the pancreas: a con-
sensus study. Virchow Arch 447: 794-799, 2005.
10. Tsuchikawa T, Hirano S, Tanaka E, et al. Modified duodenum-
preserving pancreas head resection for low-grade malignant lesion
in the pancreatic head. Pancreatology 13: 170-174, 2013.
11. Adsay NV, Adair CF, Heffess CS, et al. Intraductal oncocytic pap-
illary neoplasms of the pancreas. Am J Surg Pathol 20: 980-994,
1996.
12. Liszka L, Pajak J, Zielinska-Pajak E, et al. Intraductal oncocytic
papillary neoplasms of the pancreas and bile ducts: a description
of five new cases and review based on a systematic survey of the
literature. J Hepatobiliary Pancreat Sci 17: 246-261, 2010.
13. Marchegiani G, Mino-Kenudson M, Ferrone CR, et al. Oncocyty-
type intraductal papillary mucinous neoplasms: a unique malignant
pancreatic tumor with good long-term prognosis. J Am Coll Surg
220: 839-844, 2015.
14. D’Onofrio M, De Robertis R, Martini PT, et al. Oncocytic intra-
ductal papillary mucinous neoplasms of the pancreas. Imaging and
histopathological findings. Pancreas 45: 1233-1242, 2016.
Yamaguchi H, Shimizu M, Ban S, et al. Intraductal tubulopapillary neoplasms of the pancreas distinct from pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. Am J Surg Pathol 33: 1164-1172, 2009.

Kolby D, Thilen J, Andersson R, et al. Multifocal intraductal tubulopapillary neoplasm of the pancreas with total pancreatectomy: report of a case and review of literature. Int J Clin Exp Pathol 8: 9672-9680, 2015.

Furukawa T, Hatori T, Fujita I, et al. Prognostic relevance of morphological types of intraductal papillary mucinous neoplasms of the pancreas. Gut 60: 509-516, 2011.

Mino-Kenudson M, Castillo CF, Baba Y, et al. Prognosis of invasive intraductal papillary mucinous neoplasm depends on histological and precursor epithelial subtypes. Gut 60: 1712-1720, 2011.

Distler M, Kersting S, Niedergethmann M, et al. Pathohistological subtype predicts survival in patients with intraductal papillary mucinous neoplasm (IPMN) of the pancreas. Ann Surg 258: 324-330, 2013.

Wohlauer MV, McManus M, Fukami N, et al. Intraductal oncocytic papillary neoplasms of the pancreas: Report of a case requiring completion pancreatectomy. JOP 14: 77-80, 2013.

Marchegiani G, Mino-Kenudson M, Ferrone CR, et al. Patterns of recurrence after resection of IPMN. Who, When, How? Ann Surg 262: 1108-1114, 2015.

Kuboki Y, Shimizu K, Hatori T, et al. Molecular biomarkers for progression of intraductal papillary mucinous neoplasm of the pancreas. Pancreas 44: 227-235, 2015.

Basturk O, Tan M, Bhanot U, et al. The oncocytic subtype is genetically distinct from other pancreatic intraductal papillary mucinous neoplasm subtypes. Mod Pathol 29: 1058-1069, 2016.