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CASE REPORT

Intraductal Oncocytic Papillary Neoplasm Having Clinical Characteristics of Mucinous Cystic Neoplasm and a Benign Histology

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ABSTRACT

Context An intraductal oncocytic papillary neoplasm is a rare pancreatic tumor which was first described by Adsay *et al*. in 1996. It has been defined as a new subgroup of IPMN.

Case report We report the case of a 76-year-old woman who presented with nausea. Imaging studies revealed a cystic mass in the body of the pancreas. She underwent a successful distal pancreatectomy and splenectomy, and has subsequently remained well. Microscopically, the cyst was lined by columnar epithelium similar to pancreatic duct epithelium, and the nodular projection consisted of arborizing papillary structures, lined by plump cells with abundant eosinophilic cytoplasm. These eosinophilic cells were immunohistochemically positively stained with anti-mitochondrial antibody. The cellular atypism was mild and the proliferating index was low, compatible with adenoma of an intraductal oncocytic papillary neoplasm. Although no ovarian type stroma was identified, in our case, no communication to main pancreatic duct (located in the pancreatic body) and rapid growth by intracystic hemorrhage were clinical characteristics of a mucinous cystic neoplasm, but not IPMN.

Conclusion With only 17 cases reported to date, the clinical and pathological details of an intraductal oncocytic papillary neoplasm are still unclear. We herein add one case with different characteristics from those of the past reports. To our knowledge, this is the first case report of an intraductal oncocytic papillary neoplasm with the clinical characteristics of a mucinous cystic neoplasm.

INTRODUCTION

Oncocyte is the generally accepted term for cells exhibiting a phenotype which features an abundant eosinophilic granular cytoplasm and ultrastructurally an increase in the number of mitochondria.

In 1932 Jaffe [1] introduced the term oncocytoma to designate a tumor of the salivary glands which predominantly consisted of oncocytes. Although oncocytomas have since been reported in other organs including the thyroid, parathyroid and pituitary glands, the kidney, the ovaries and lungs, tumors predominantly composed of oncocytic cells in the pancreas are extremely rare [2]. Adsay *et al*. [3] proposed a new disease entity known as an intraductal oncocytic papillary neoplasm (IOPN) of the pancreas in 1996. With only 17 cases reported

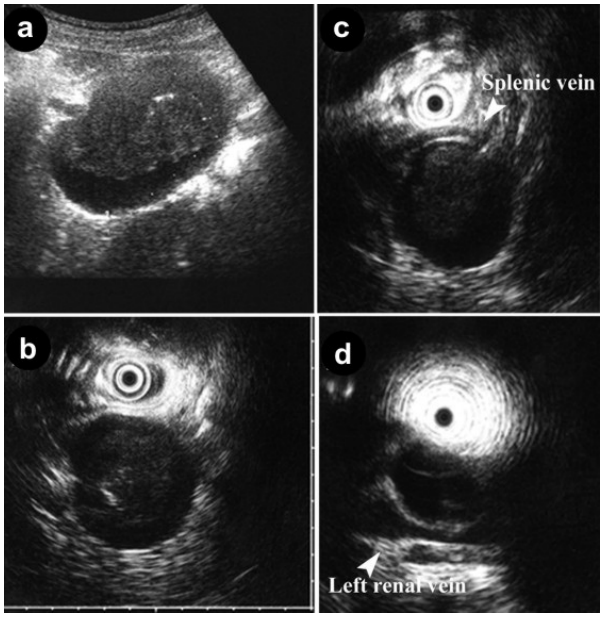

Figure 1. a. Abdominal ultrasonography revealing a monolocular, apparently cystic mass in the body of the pancreas. This mass contained a 30 mm nodule with a high echo spot, indicating calcification. Endoscopic ultrasonography showed findings similar to ultrasonography (**b.**) and displacement of the splenic (**c.**) and left renal veins (**d.**).

to date, the clinical and pathological details of IOPNs are still unclear. We herein add one case with different characteristics from those of past reports. To our knowledge, this is the first case report of IOPN with clinical characteristics of a mucinous cystic neoplasm (MCN).

CASE REPORT

A 76-year-old woman presented at our hospital in December 2005 complaining of nausea. Abdominal ultrasonography (US) and enhanced computed tomography (CT) revealed a cystic mass with a maximum diameter of approximately 40 mm located in the body of the pancreas. At the time, she rejected the recommendation for further examinations. Three months later, in March 2006, she was hospitalized when a second CT showed that the rapidly growing cystic mass had a maximum diameter of approximately 60 mm. Her family history and past history were unremarkable. On physical examination, she was 156 cm tall and weighed 62 kg; blood pressure was 120/74 mmHg; pulse was 70 beats/min; and body temperature was 36.4 ºC. There were no abnormal findings in the chest or abdomen.

Laboratory data at admission were within the normal ranges, including peripheral blood leukocyte count (5,550 μL^{-1}, reference range: 3,800-8,000 μL^{-1}), hematocrit (37.1%, reference range: 36.0-52.0%), total bilirubin (0.5 mg/dL, reference range: 0.1-1.0 mg/dL), transaminase (asparatate aminotransferase, AST, 16 IU/L, reference range: 1-38 IU/L; alanine aminotransferase, ALT, 7 IU/L, reference range: 2-40 IU/L), alkaline phosphatase (208 IU/L, reference range: 111-336 IU/L), and serum amylase (163 IU/L, reference range: 54-168 IU/L). Tumor markers were also normal with regard to carcinoembryonic antigen (2.4 ng/mL, reference range: 0-5.0 ng/mL) and carbohydrate antigen CA 19-9 (11.7 U/mL, reference range: 0-37.0 U/mL).

US and endoscopic ultrasonography (EUS) revealed a monolocular cystic mass of approximately 60 mm in the body of the pancreas which contained a 30 mm nodule with a high echo spot indicating calcification, and displacing the splenic and left renal veins (Figure 1). Enhanced CT (Figure 2) showed that the nodular region inside the monolocular cystic mass had a slightly higher density than

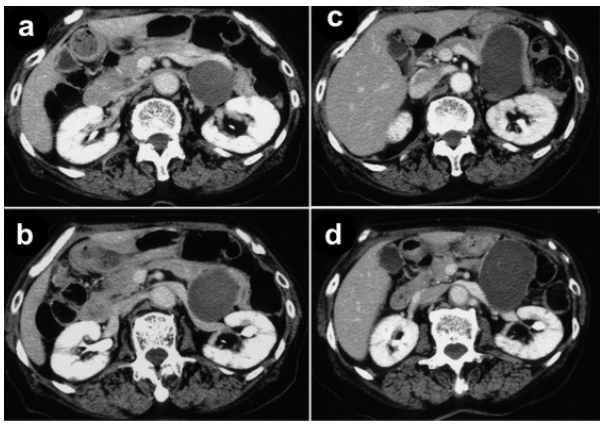

Figure 2. Enhanced CT images from December 2005 (**a.**, **b.**) and March 2006 (**c.**, **d.**). Enhanced CT shows a monolocular cystic mass with a higher density nodule relative to a cystic region which was not enhanced. The rapid growth of the mass was determined by comparing the findings from December 2005 to those of March 2006. Displacement of the splenic and left renal veins was found as well in the findings of endoscopic ultrasonography.

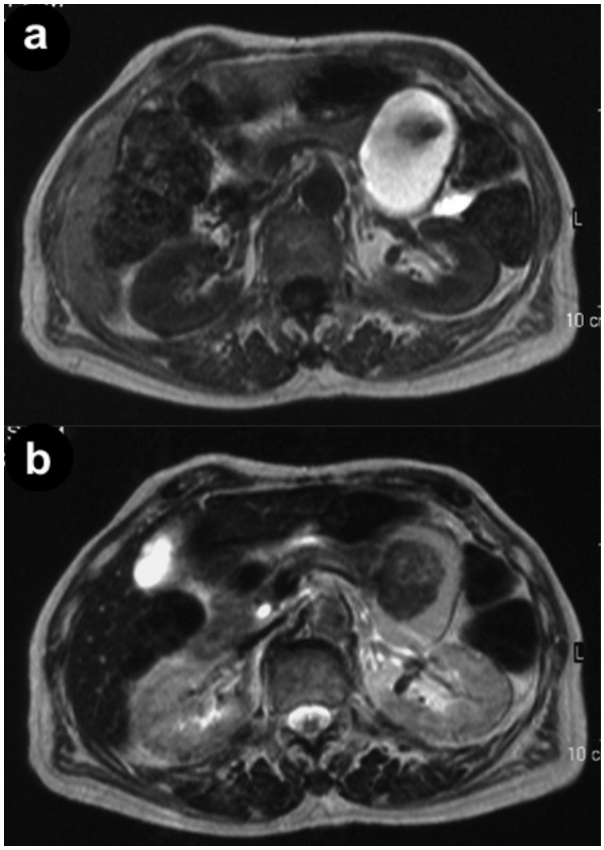

Figure 3. Magnetic resonance imaging revealed very high signal intensity in T1-weighted images of the cystic region (**a.**) and high signal intensity in T2-weighted images (**b.**). The nodular region showed a mixture of high and low signal intensities in T2-weighted images.

the cystic region and was not enhanced. The rapid growth of the mass was assessed by comparing findings from March 2006 with previous images from December 2005. Displacement of the splenic and left renal

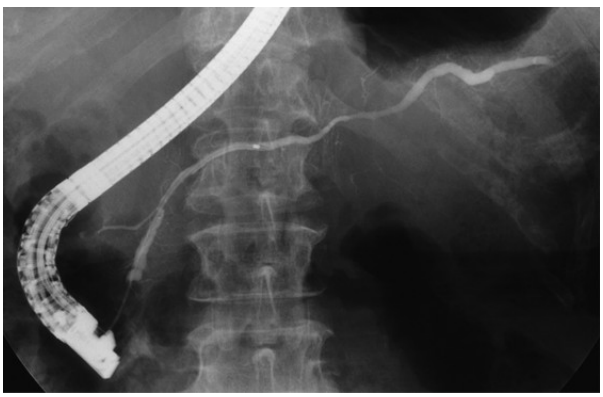

Figure 4. Endoscopic retrograde pancreatography images of stenosis of the main pancreatic duct in the body of the pancreas. No communication between the mass and the main pancreatic duct was detected.

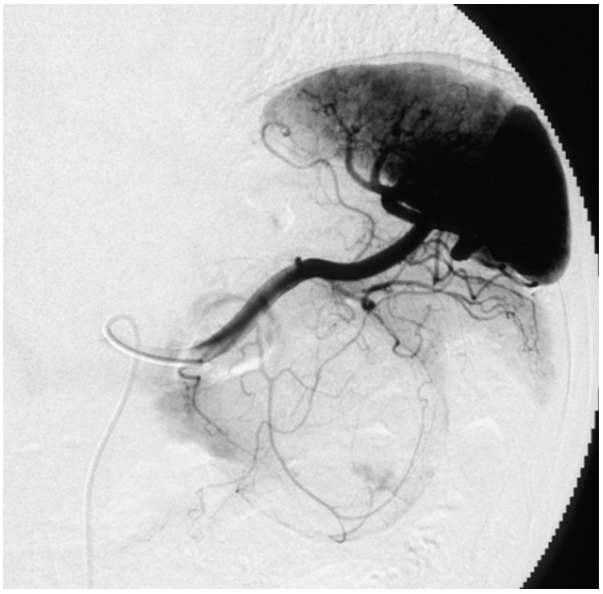

Figure 5. Splenic arteriography revealed displacement by the tumor, but no encasement and tumor stain.

veins was detected as well as findings of EUS. Magnetic resonance imaging revealed that the cystic region generated very high signal intensity on T1-weighted images and high signal intensity on T2-weighted images whereas the nodular part showed a mixture of high and low signal intensities on T2-weighted images (Figure 3). Endoscopy showed that the orifice of the papilla of Vater was normal. Endoscopic retrograde cholangiopancreatography (ERCP) showed stenosis of the main pancreatic duct (MPD) in the body of the pancreas, and mild dilatation of the MPD in the tail. Furthermore, no communication between the mass and the MPD was found (Figure 4). Splenic arteriography did not reveal any encasement or tumor stain, but displacement by the tumor (Figure 5).

Based on the findings of these examinations, a diagnosis of MCN with hemorrhagic contents was suspected, and a distal pancreatectomy and splenectomy was performed in April 2006. The surgically resected specimen showed a well-demarcated cystic mass measuring 75x55x50 mm in size and located in the body of the pancreas (Figure 6a). On sectioning, the cystic tumor contained brownish mucous and jelly-like material consisting of blood coagulation with fibrin deposition, which was detected by

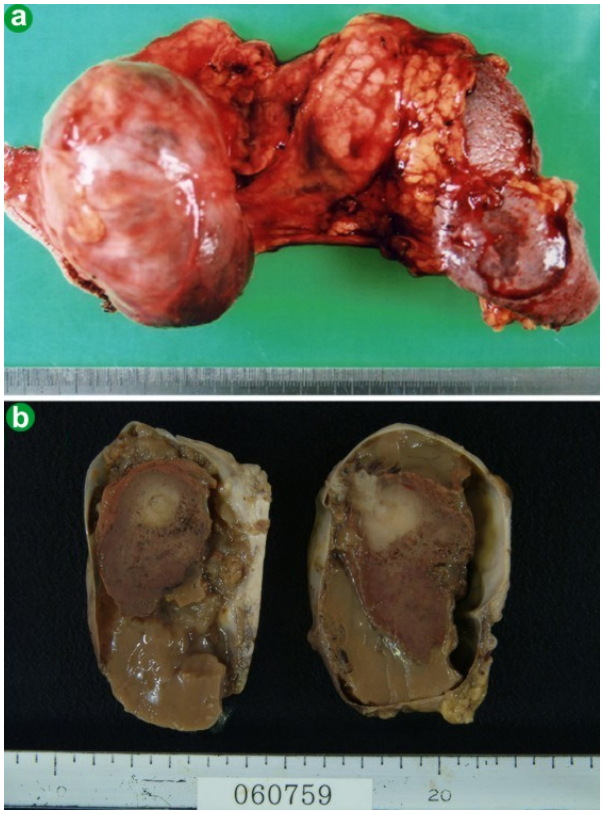

Figure 6. An image of the surgically resected specimen, showing a cystic mass in the body of the pancreas (**a.**). Upon sectioning, the cystic tumor and the monolocular cysts contained blood coagulation with fibrin deposition, mucous and a nodular papillary projection measuring 10 mm in diameter (**b.**).

image examinations. Macroscopic findings indicated that the rapid growth within the short period observed in our case was due to internal hemorrhaging, which is sometimes observed in MCNs, but not intraductal papillary mucinous neoplasms (IPMNs). In addition, there was a nodular papillary projection measuring 10 mm in diameter in the cystic wall (Figures 6b and 7a). Microscopically, the cystic wall was lined by columnar pancreas duct epithelium with occasional micropapillary projections and the nodule was characterized by variably complex, arborizing papillary structures lined with plump cells containing abundant eosinophilic cytoplasm (Figure 7bc). Immunohistochemically, the oncocytic tumor cells stained positively with anti-mitochondrial antibody 113-1 used at a dilution of 1:400 (BioGenex, San Ramon, CA, USA) (Figure 7d). An ovarian-type stroma, a hallmark of MCN, was not found. These pathologic findings led to a diagnosis of IOPN. The low mitotic rate having a mindbomb homolog-1 index of less than 1% and the mild degree of cyto-architectural atypia warranted the classification of adenoma.

The patient had an uneventful postoperative course. At a 9 month follow-up examination, she was well and without symptoms or evidence of tumor recurrence.

DISCUSSION

Pancreatic tumors with oncocytes have been described as oncocytic changes in endocrine tumors [4] or solid and papillary epithelial tumors [5], or as coming from chronic pancreatitis [6], but they are uncommon with intraductal or cystic tumors of the pancreas. In 1996, Adsay *et al*. [3] reported a new subgroup of IPMNs. They proposed a new disease entity known as IOPN, which was defined by the following pathologic features: Pancreatic duct lesions signifying complex, arborizing, and proliferating papillary structures, tumor cells with a finely granular, eosinophilic cytoplasm, and diffusely present goblet cells. In addition, the cytoplasm of tumor cells stains diffusely with anti-mitochondrial antibodies. Electron

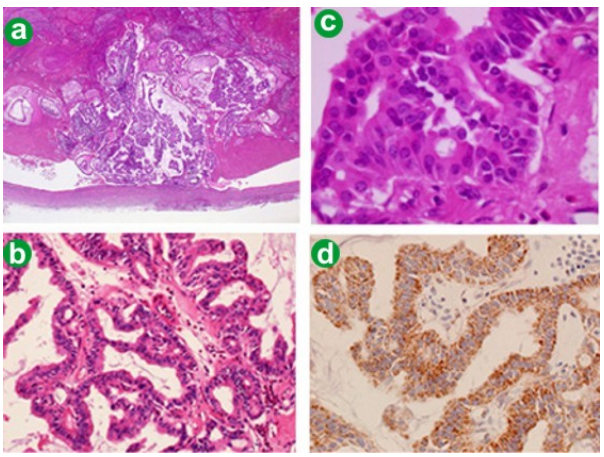

Figure 7. Microscopically, the cyst wall was lined by columnar pancreas duct epithelium with papillary projections (**a.** x20), and the papillary tumor was characterized by variably complex, arborizing structures which were lined by plump cells with abundant eosinophilic cytoplasm (**b.** x100, **c.** x400). Immunohistochemically, the cytoplasm of the tumor cells was filled with anti-mitochondrial antibody (**d.** x100).

microscopy images show abundant tumor cell cytoplasm rich with mitochondria.

The underlying cause for the increased numbers of mitochondria in oncocytoma has been the subject of several reports. Welter *et al*. [7] measured an increase in mitochondrial deoxyribonucleic acid (DNA) aberrations which were not accompanied by a parallel rise in mitochondrial ribonucleic acid (RNA) transcripts. These findings, which are compatible with the presence of poorly functioning or nonfunctional mitochondria in oncocytic neoplasms, suggest that the excess of mitochondria may be due to a partial block of mitochondrial RNA transcription or decreased RNA stability. Thus, although the biogenesis of mitochondria in oncocytic cells is obviously abnormal, the relationship of this phenotype to the development of tumors remains obscure [2].

The 17 cases of IOPN which have been reported are summarized in Table 1 [3, 8, 9, 10, 11, 12, 13, 14]. The average age of the patients was 62.5 years, and the male-to-female ratio was 9:8. In cases in which the chief complaint was known, epigastralgia and discomfort were most common while diabetes mellitus and pancreatitis were frequent as coexisting symptoms. As in cases of IPMN, most tumors (72.2%) were located in the pancreatic head while a few were found in the body or tail. Tumor size was relatively large, with an average diameter of 62.5 mm.

Because reports of IOPN are found primarily in pathology journals, detailed analyses of image studies such as ERP and EUS have not been carried out. Only four case reports clearly mention the use of ERP to analyze communication as it relates to the main

Table 1. Summary of past reports on IOPN in the English literature.

Case	Author, year	Age	Sex	Symptoms	Location	Size (mm)	Diagnosis
1	Adsay *et al*., 1996 [3]	52	M	Abdominal pain, DM	Head	16	Carcinoma
2	Adsay *et al*., 1996 [3]	78	F	Diarrhea, DM for 20 years	Head; body/tail	40; 100	Carcinoma
3	Adsay *et al*., 1996 [3]	73	F	Bloating, long history of DM	Head	60	Carcinoma
4	Adsay *et al*., 1996 [3]	69	M	Incident during CT for prostate	Tail	60	Carcinoma
5	Adsay *et al*., 1996 [3]	62	F	Gastric "pressure", nausea, high blood glucose	Head, body	70	Carcinoma
6	Adsay *et al*., 1996 [3]	65	M	IVC obstruction, DM for years	Head	130	Carcinoma
7	Adsay *et al*., 1996 [3]	39	M	Pancreatitis for 4 mo	Head	40	Carcinoma
8	Adsay *et al*., 1996 [3]	66	M	Pancreatitis	Body, tail	150	Carcinoma
9	Adsay *et al*., 1996 [3]	74	M	Pancreatitis	Head	25	Carcinoma
10	Adsay *et al*., 1996 [3]	64	F	Epigastric discomfort	Head	55	Carcinoma
11	Adsay *et al*., 1996 [3]	43	F	Epigastric discomfort	Head	20	Carcinoma
12	Jyotheeswaran *et al*., 1998 [8]	69	F	Upper and epigastric abdominal discomfort	Head	58x47x37	Carcinoma
13	Thompson *et al*., 1998 [14]	37	M	Body weight loss, early satiety, malaise, abdominal discomfort	Head	120x100x80	Carcinoma
14	Nobukawa *et al*., 1999 [12]	51	M	Health check	Head	ND	Carcinoma
15	Patel *et al*., 2002 [10]	73	M	Recurrent pancreatitis	Tail	25	Carcinoma
16	Noji *et al*., 2002 [13]	68	F	Fatty liver	Tail	12x65x49	Carcinoma
17	Shima *et al*., 2005 [9]	79	F	Epigastralgia	Head	28x21	Borderline malignancy
18	Present case, 2007	76	F	Nausea	Body	75x55x50	Adenoma

Continues ……

Table 1. Continued.

Case	Metastasis	Monolocular or multilocular	Operation	Prognosis
1	None	ND	Subtotal pancreatectomy	Alive, 3 years
2	None	ND	Total pancreatectomy	Died on 12th postoperative day
3	None	ND	PD, completion pancreatectomy after recurrence	Recurrence after 2 years; died with NED after 5 years
4	Liver?	ND	Distal pancreatectomy	Died on 15th postoperative day
5	None	ND	PD	Alive, 7 months
6	None	ND	PD	Died with NED, 2.5 years
7	None	ND	PD	Alive, NED at 3 years
8	None	ND	Distal pancreatectomy	Alive, NED at 5 months
9	None	ND	PD	Alive and well, 1 month
10	None	ND	PD	Alive and well, 1 month
11	None	ND	PD	Alive and well, 1 month
12	None	Multilocular	Whipple's procedure (PD)	Alive and well, 1 year
13	Liver	Multilocular	Transplant surgery ?	ND
14	Lymph node	Monolocular	PD	Died from postoperative complication
15	Liver	ND	Distal pancreatectomy and splenectomy	Died from a recurrence after 4 years
16	None	Multilocular	Distal pancreatectomy	Alive, NED at 15 months
17	None	Multilocular	PD	Alive, NED at 3 years
18	None	Monolocular	Distal pancreatectomy	Alive, NED at 9 months

CT: computed tomography
DM: diabetes mellitus
IVC: inferior vena cava
ND: not described
NED: no evidence of disease
PD: pancreaticoduodenectomy

pancreatic duct [8, 9, 10, 13]. Adsay *et al*. [3] reported that mucin production in IOPNs was less than in IPMNs. To date, reports of dilatation of the MPD or mucin excretion from the duodenal papilla are limited [8, 9]. In our particular case, no communication between the mass and the MPD was found in ERCP or pathological findings, and neither dilatation of the MPD nor excretion of mucin from the papilla could be detected. In addition, the cystic contents with hemorrhage in the present case are often observed in MCNs but not IPMNs [15, 16]. Therefore, in our case, the IOPN shared clinical characteristics with the MCN as to location, internal hemorrhaging and no communication with the MPD unlike past reports.

Ninety-four percent of cases were diagnosed as carcinoma including reports of invasive tumors or distant metastasis. Therefore, the case presented here is a rare example of a benign IOPN. An adenoma-carcinoma sequence has been proposed for IPMN, and the issue of malignant potential is under intense investigation [17]. In contrast, the degree of malignant potential for IOPNs is still unclear due to the scarce number of reports. As oncocytic tumors tend to be benign in other organs, it is thought that the presence of oncocytes is not the main deciding factor in determining the malignant potential of a tumor [2]. Because all the reported cases of IOPNs were surgical cases, the average size and malignancy in these

cases may be biased toward larger size and higher malignancy. Because only one case involved death due to an IOPN, good prognoses can be expected. However, it may be necessary to consider the suitability of follow-up periods which up to now have been short.

In conclusion, the present case had different characteristics from the IOPNs of past reports. The clinical significance of an IOPN is unclear due to the scarce numbers of reports but warrants further examination.

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Keywords Adenoma; Oxyphil Cells; Pancreas

Abbreviations IOPN: intraductal papillary oncocytic neoplasm; MCN: mucinous cystic neoplasm; MPD: main pancreatic duct

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