Cytopathologic Diagnosis of Oncocytic Type Intraductal Papillary Mucinous Neoplasm: Criteria and Clinical Implications of Accurate Diagnosis

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Abstract

BACKGROUND—Cytologic findings of pancreatic oncocytic-type intraductal papillary mucinous neoplasms (IPMNs)/intraductal oncocytic papillary neoplasms (IOPNs) are largely unknown.

METHODS—Five IOPNs encountered by the authors were analyzed.

RESULTS—Four IOPNs were located in the pancreatic head, and 1 was located in the pancreatic body/tail in 2 men and 3 women ages 56 to 84 years (mean age, 66 years). Radiologic diagnoses included pancreatic ductal adenocarcinoma (PDAC) in 2 patients, invasive cancer associated with IPMN in 1 patient, IPMN versus mucinous cystic neoplasm in 1 patient, and cystic mass in 1 patient. Cytologic findings included: hypercellular smears (4 of 5 cases) containing well formed clusters of oncocytic cells (5 of 5 cases) with prominent, slightly eccentric nucleoli (4 of 5 cases), predominantly arranged in sheets/papillary units (5 of 5 cases), with punched-out intercytoplasmic spaces (4 of 5 cases), and with occasional 3-dimensional groups and focal necrosis (3 of 5 cases). The intracytoplasmic mucin and thick extracellular mucin typical of other IPMNs were observed only in 2 cases and were very limited. The mean size on resection was 4.5 cm. Invasion was observed in 3 cases (0.1, 0.3, and 2.0 cm) of tubular-type IPMN. Initial cytologic evaluation was performed by the authors in 4 of 5 cases, which were diagnosed as IOPN (n = 3) and IPMN versus cystic PDAC (n = 1). One case was initially misdiagnosed as PDAC and, on resection, proved to be noninvasive IOPN.

CONCLUSIONS—Cytopathologic features of IOPNs are classical, similar to their histologic counterparts, and differ significantly from other IPMN subtypes. Because of their highly complex appearance, they are often radiologically misdiagnosed as PDAC; thus, failure to recognize their characteristic features on fine-needle aspiration may lead to inappropriate treatment. Patients with IOPN have an incomparably better prognosis than patients with ordinary PDAC, even when their neoplasms are invasive.

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CONFLICT OF INTEREST DISCLOSURES
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INTRODUCTION

The vast majority of clinically relevant pancreatic masses are pancreatic ductal adenocarcinomas (PDACs), which have a dismal prognosis and a 5-year survival rate of less than 5%. PDAC is currently the fourth (and is estimated to become the third) leading cause of cancer-related death in the United States. More Americans die of pancreatic cancer than prostate cancer, and it is estimated that, in 2015, pancreatic cancer will surpass breast cancer as the third leading cause of cancer mortality in the United States. Because of its relative frequency and dire clinical consequences, the foremost task in the differential diagnosis of pancreatic lesions is the exclusion of PDAC; and, if it is radiologically complex, the case is typically assigned this diagnosis.

The vast majority of PDACs present as solid lesions; consequently, PDAC is seldom considered in the differential diagnosis of cystic pancreatic lesions, which are increasingly being encountered in clinical practice. In fact, because of advances in imaging technology, incidental pancreatic cysts are discovered in nearly 14% of the elderly. Fortunately, most cystic pancreatic lesions are either benign or low-grade malignant neoplasms. The most common cystic pancreatic neoplasms are intraductal papillary mucinous neoplasms (IPMNs), which are defined as cystic, mass-forming, intraductal tumors characterized by proliferating, mucinous epithelium and result in cystic dilatation of the main and/or branch ducts. Similar to PDACs, IPMNs typically arise in patients aged ≥60 years and are much more common in the pancreatic head. Although the vast majority of IPMNs present as innocuous-appearing cystic lesions, a subset (the entity originally described as intraductal oncocytic papillary neoplasm [IOPN] and now classified as the oncocytic variant of IPMN in the 2010 World Health Organization series), frequently presents as complex tumors that are often clinically interpreted as cancerous. However, recent studies indicate that, in fact, IOPNs are quite different from IPMNs not only in their clinical presentation but also at the molecular level. In this report, we present cytologic findings from 5 examples of the oncocytic variant of IPMN (also known as IOPN) in which an accurate cytologic diagnosis on fine-needle aspiration biopsy (FNAB) was crucial in ensuring proper patient management and avoiding detrimental chemoradiation.

MATERIALS AND METHODS

Of 2600 pancreatectomy specimens from 1979 to 2014 that included 1690 adenocarcinomas (and variants) as well as 185 verified IPMNs (including 10 resected IOPNs), 5 specimens had cytologic material available for analysis. In addition, 11 IOPNs that were originally reported by 1 of the authors (V.A.) in 1996 (from the files of Memorial Sloan-Kettering Cancer Center) were also reviewed, but none of those had FNAB material available, probably because of incomplete clinical histories or because most were from an era (before...
All patients underwent endoscopic ultrasound-guided FNAB with rapid on-site evaluation (ROSE) and 3 to 6 passes per patient (mean, 3.7 passes per patient), all of which were deemed adequate. Cyst fluid analysis and molecular studies were not performed on any of the specimens.

All slides of the cytology specimens were reviewed. On average, 7 slides were available per case (range, 2-19 slides per case), including both Papanicolaou-stained slides (range, 1-8 per case) and Diff-Quik–stained slides (range, 1-8 per case). Cell-block sections were available for review in 4 of 5 cases.

All 5 follow-up resection specimens were reviewed by the authors. For the consultation cases, follow-up clinical information was obtained from the submitting outside pathologists.

The clinicocytopathologic characteristics of the 5 cases were compared with the findings documented in the literature for ordinary (nononcocytic) IPMNs, including our own publications in which we documented both the clinical and pathologic features of nononcocytic IPMNs and also performed a separate, focused analysis of the distinct subtypes.

**RESULTS**

**Clinical Characteristics**

The 5 patients included 2 men and 3 women who ranged in age from 56 to 84 years (mean age, 66 years). Four patients had tumors arising in the pancreatic head, and 1 patient had a tumor arising in the pancreatic body/tail.

**Radiologic Findings**

Tumors ranged in size from 2.5 to 6.6 cm (mean size, 4.5 cm) and had radiologic diagnoses of PDAC (n = 2; cases 1 and 5); mucinous cystic neoplasm versus IPMN (n = 1; case 4); main duct-IPMN with invasive component (n = 1; case 2); and cystic mass, not otherwise specified (n = 1; case 3). It is noteworthy that only case 2 was definitively diagnosed as IPMN on imaging (based on marked dilatation of the main pancreatic duct [3.3 cm]) and was also interpreted as having an invasive component on imaging, but it proved to be noninvasive on resection. Clinicopathologic and radiologic findings are summarized in Table 1.

**Cytologic Findings**

Diff-Quik smears were hypercellular in the majority of cases (4 of 5 cases; 80%), and limited amounts of thick magenta or blue extracellular mucin were present in the smear background in only 2 of 5 cases (40%). Neoplastic cells were observed predominantly in large, flat sheets (100% of cases) with only minimal crowding and occasional papillae (Fig. 1). In some areas, there were 3-dimensional groups (3 of 5 cases; 60%) with complex branching, papillary configuration (100%), and focal fibrovascular cores (80%) (Fig. 1). All
5 cases had numerous neoplastic cells that displayed oncocytic features (Fig. 2). These cells were intermediate to large with well defined borders, dense granular cytoplasm, large central nuclei with predominantly rounded nuclear borders, and prominent but relatively small, slightly eccentric nucleoli (100%) (Fig. 2). Intracytoplasmic mucin was not readily evident but was identifiable on careful inspection in 4 of 5 cases (80%) (Fig. 3). Focal oncocytic cells were observed in the extracellular mucin and smear background in 30% of cases, indicative of cyst contents (Fig. 4). Necrotic debris was observed in the smear background in 3 of 5 cases (60%). Single, intact oncocytic cells were identified in 4 of 5 cases (80%), and rare psammomatous calcifications were observed in the smear background of case 5.

Papanicolaou-stained smears and ThinPrep slides revealed large oncocytic cells, some with ill-defined cell borders and a vague, syncytial arrangement (Figs. 2, 3). The cells had dense, granular cytoplasm and round-to-oval central nuclei with prominent, slightly eccentric nucleoli. Cytoplasmic granules ranged in color from greenish-blue to orange-pink (Figs. 2, 5). Chromatin was relatively fine and homogenous but ranged from predominantly hyperchromatic in most cases to hypochromatic in others (Fig. 2). Nuclei were predominantly round and smooth, but nuclear irregularity was appreciable in 2 cases (cases 2 and 5) (Figs. 4, 5; Table 2). Despite their overt cellularity and striking architectural complexity with sheet-like or papillary configuration, cytologically, the tumor cells displayed some degree of uniformity. Conversely, on careful inspection, anisonucleosis could also be observed focally in 4 of 5 cases (80%; mild in cases 2 and 3 and marked in case 5). Case 5 also had hyperchromatic nuclei, a high nuclear-to-cytoplasmic ratio, and single-cell and background necrosis (Fig. 5), and it had an invasive (<2 cm) component on resection. Punched-out intercytoplasmic spaces (Fig. 3) were observed focally within sheets. Most of these were empty and did not contain mucin. However, intracytoplasmic mucin was identified in occasional tumor cells (Fig. 3).

Cell blocks were available for review in 4 of 5 cases and were very helpful in supporting the diagnosis, because they often revealed arborizing papillae (some with striking basophilic edema) lined by large oncocytic cells (Figs. 4, 5). Mitotic figures and ovarian-type stroma were not observed on smears or cell blocks. Single-cell necrosis and areas of confluent necrosis were present in only 1 case (case 5), in which invasive carcinoma was identified on resection.

At the time of ROSE, 2 cases (cases 1 and 5) were called suspicious for adenocarcinoma. One (case 1) went on to be called PDAC (with a possible intraductal component) on final cytologic diagnosis (Fig. 4), but it proved to have no invasive component on resection. Final cytology diagnoses were made by the authors in the other 4 cases (80%) and included neoplastic cells present: oncocytic-type IPMN with high-grade atypia in 3 of 4 cases (75%; cases 3-5; all 3 were radiologically cystic) and neoplastic cells present: IPMN versus cystic pancreatic ductal adenocarcinoma in a single case (25%; case 2). For case 5, the diagnosis of suspicious for invasion was rendered in the original report based on the marked anisonucleosis, 3-dimensional clusters, and extensive single-cell and background necrosis/diathesis, features typically observed in invasive carcinomas. However, cases with such findings may be better classified as having features suspicious for the development of frank adenocarcinoma, because invasion cannot be definitively identified on cytologic specimens.
This case proved to be multifocal invasive carcinoma with lymph node metastasis on resection. Cytologic findings are summarized in Table 2.

**Histologic Findings**

Resections included pancreatectoduodenectomy (n = 4) and distal pancreatectomy (n = 1). On gross examination, tumors ranged in size from 2.2 to 6.5 cm (mean size, 4.5 cm) and were mostly composed of demarcated nodules of relatively soft, tan, friable, granular material that corresponded histologically to abundant intraductal papillary nodules with intervening atrophic/fibrotic pancreatic tissue (Figs. 3, 6).

Morphologically, all cases exhibited classic features of oncocytic IPMN (IOPN), with exuberant, complex, arborizing papillae and delicate fibrovascular cores lined by 2 to 5 cell layers of cells with distinctive oncocytic cytology (abundant acidophilic, granular cytoplasm; round nuclei; and single, prominent, eccentric nucleoli). Characteristic punched-out intercellular lumina formation was noted in all 5 cases (Fig. 3). Four cases were pure oncocytic IPMNs, whereas 1 (case 2) had an additional gastric-foveolar–type epithelial component (n = 1). All 4 resected IOPNs were graded (by default) as high-grade dysplasia, because of their cytoarchitectural complexity, nuclear enlargement and/or membrane irregularity, and nucleolar prominence. In addition, 3 of 5 cases (60%) had an invasive carcinoma component with a mean size of 0.8 cm (range, 0.1-2.0 cm). The invasive carcinoma component was of the tubular type (ordinary PDAC) in 2 cases but had focal extravasated stromal mucin in 1 case (Table 1). All margins were negative for invasive carcinoma, but 1 (case 2) had margin involvement by IPMN, and another (case 5) had lymph node metastasis (with 5 positive lymph nodes of 17 lymph nodes examined). Of the remaining 4 (cases 1-4), 18, 19, 14, and 23 negative lymph nodes were examined, respectively.

**Follow-Up Information**

Follow-up information was available for 4 patients (cases 1, 2, 4, and 5) and ranged from 23 days to 38 months. Patient 4 died of perioperative complications (pneumonia and intra-abdominal bleeding) 23 days after resection. At the last follow-up, all other patients (cases 1, 2, and 5) were alive with no evidence of disease, and patient 5 had completed 6 courses of chemotherapy. Patient 3 was lost to follow-up after surgery.

**DISCUSSION**

The oncocytic variant of IPMN, also known as IOPN, was first described in 1996 as a fairly distinct type of pancreatic tumor. Its entity-defining histomorphology is characterized by complex, arborizing, intraductal papillae lined by oncocytic epithelial cells containing mitochondria-rich eosinophilic cytoplasm and large nuclei with prominent, eccentric nucleoli and intercellular spaces, which sometimes impart an almost cribriform appearance to the epithelium.

Because the papillary nodules that characterize these tumors are believed to represent proliferating intraductal processes, they have been designated IOPNs. Because they are intraductal and papillae-forming, they share several features with IPMNs and, thus, were
included as a subset of IPMN in the 2010 World Health Organization classification, although the merit of this approach is now rightfully being questioned,8 because these oncocytic examples actually have various features that distinguish them from other IPMN epithelial subtypes (see Table 3).6,7,9,10,13 Mucin production is typically minimal and unimpressive; and, unlike intestinal-type (and other main-duct) IPMNs, virtually none of the oncocytic examples present with mucin extrusion from the ampulla of Vater. In addition, in contrast to gastric (and other branch-duct) IPMNs, these cases almost never present as innocuous cystic lesions. Instead, they typically form complex masses with solid and cystic components, and significant numbers are diagnosed radiologically as cystadenocarcinoma or PDAC with cystic change, as were 2 of our cases. An additional case had a highly infiltrative cancerous process as a part of its radiologic assessment but proved to be minimally invasive (with lymph node metastasis at resection). Another unique and interesting feature of IOPNs is their low/normal carcinoembryonic antigen levels, unlike other IPMN subtypes.15

In addition to being highly complex and nodular and, thus, closely mimicking PDAC even when they are noninvasive, IOPNs may also harbor invasive carcinoma. In our series, a convincing invasive carcinoma component was observed in 3 cases, which is in accordance with a recent publication by Marchegiani et al, who reported that 61% of their surgical cohort of 19 patients had invasive carcinoma. However, despite their overall complexity and relatively large size (the mean size was 4.5 cm in our cohort), which causes major preoperative concern for malignancy, in fact, invasive carcinoma is typically small (mean size, 0.8 cm) in these tumors. Along with the tumor cells’ distinct biology,10,11 the small size of invasion may play a role in their surprisingly good prognosis, which is now amply illustrated in the literature and suggests that deaths from these tumors are only very rarely reported, with a 5-year survival rate >90%.9,13 For this reason, it is important to diagnose IOPNs on cytology so that patients can be appropriately treated in a thoughtfully planned fashion.

Although the cytologic features of IPMNs are well established,15,18-21 the cytologic features of IOPNs (oncocytic-type IPMNs) are described only rarely and mainly in isolated reports.19,21-23 This is probably related in part to the rarity of the entity, but it is also somewhat attributable to a lack of recognition, which we hope the current study will alleviate to some degree. It is noteworthy that, among the 21 IOPNs we encountered, only 5 had documented FNABs, but this may have been because many of these patients were from an era when pancreatic FNAB was not as common. We suspect that these lesions will be encountered increasingly in the future.

Because the preresection diagnosis of IPMN typically relies on imaging studies and a demonstration of thick mucin, and because IOPNs often lack both of these (see Table 3), it is crucial for cytopathologists to be aware of and rely on the cytomorphologic findings in these tumors, namely, their oncocytic cytology, their distinctive cellular complexity, a papillary architecture that differs from that of other IPMNs, and the presence of punched-out intercellular spaces. If such findings are encountered in a given case, then a more careful inspection with close cytoradiologic correlation would become crucial in making an accurate diagnosis and 1) ruling out other IPMN subtypes (because they are biologically and...
clinically different) but also 2) excluding ordinary PDACs, with which these tumors may be confused.

In addition to the sheets or papillary groups of characteristically large oncocytic cells with abundant granular cytoplasm, the unique cytologic features of these tumors also include their well defined cell borders, large central nuclei, prominent eccentric nucleoli, and focal intercellular punched-out spaces. Oncocytic papillae may be observed in ThinPrep solutions, smears, and cell blocks, but they are most easily appreciated on cell-block sections, which preserve papillary architecture and can better aid in diagnosis.\textsuperscript{19} In a study of cell-block material from 20 IPMNs, Monzen et al demonstrated that cell-block examination had 100% specificity in predicting IPMN subtype (including 2 oncocytic examples).\textsuperscript{19} Similar results were obtained by Hibi and colleagues, who subtyped 19 IPMNs (3 of them oncocytic) on pancreatic juice cytology.\textsuperscript{21}

For reporting of IPMNs, Pitman et al proposed the term \textit{high-grade epithelial atypia} to describe the spectrum of changes observed in neoplastic mucinous cysts with high-grade dysplasia and invasive carcinoma,\textsuperscript{24,25} which are of utmost importance in the diagnosis of these tumors. All oncocytic-type IPMNs, by default, qualify as exhibiting \textit{high-grade atypia} by virtue of their architectural and cellular complexity, large nuclei, and prominent nucleoli. However, these tumors are also strikingly monotonous, with relatively mild anisokaryosis except for more degenerative/symplastic atypia akin to that observed in oncocytic neoplasms at other sites (e.g., Hürthle cell tumors). Thus, it is not clear whether the \textit{high-grade atypia} observed in these tumors is truly reflective of a more aggressive behavior or of a different cellular biology that does not necessarily translate into a malignant outcome. Recent studies have confirmed the unexpectedly good prognosis of these neoplasms, with very few patients dying of their tumors,\textsuperscript{9,13} illustrating that the very distinct nature of these neoplasms diverges from that of both conventional IPMNs and PDACs.

\textbf{Differential Diagnosis}

Compared with mucinous cystic neoplasms and other IPMN subtypes, we and others have observed that IOPNs (oncocytic IPMNs) produce far less intracellular mucin and have less extracellular \textit{colloid-like} mucin on both cytologic and histologic examination, features typically reported in other IPMN subtypes.\textsuperscript{4-6,8,9,21} However, their distinctive oncocytic features separate them from other epithelial IPMN subtypes. A paucity of mucin combined with the cellularity and complex architecture of IOPNs, unfortunately, can lead to their misdiagnosis as PDAC, acinar tumors, pancreatic neuroendocrine tumors with oncocytic features, or metastases.

It should be kept in mind that, unlike classically cystic IPMN, oncocytic examples often have a more solid appearance on imaging, which can lead to misdiagnosis as adenocarcinoma by radiologists and gastroenterologists.\textsuperscript{13} Of the cases in our cohort, only 2 were correctly diagnosed as fundamentally intraductal neoplasms (\textit{neoplastic mucinous cysts}) on imaging, whereas 2 were suspected of being PDACs. However, it should be noted here that even the cases that were radiologically interpreted as solid (suspect PDAC) were diagnosable as IOPNs because of their distinctive cytomorphic features. It is also worth noting that an interesting radiologic feature of oncocytic IPMNs is their high uptake on
positron emission tomography, likely because of the oncocytic cells’ high metabolic activity.\textsuperscript{26,27} The latter is potentially exploitable in their radiologic distinction from PDACs and other IPMN subtypes.\textsuperscript{28}

Because of their complexity, large size, and often solid appearance, IOPNs are prone to be misdiagnosed clinically as cystic PDACs, as in 2 of our cases. Attention to the cytopathologic characteristics elucidated in this study should allow the distinction of these tumors from PDAC. PDAC often exhibits cytologic features of frank adenocarcinoma, including 3-dimensional clusters and singly dispersed malignant cells with high nuclear-to-cytoplasmic ratio, 4-fold anisonucleosis, marked nuclear irregularity, cytoplasmic mucin vacuoles, and background necrosis. In contrast, IOPNs have relatively monotonous cells and the distinctive cytology of abundant, acidophilic, granular cytoplasm and nuclei with single, prominent eccentric nucleoli in a backdrop of relatively uniform, pale chromatin. IOPNs also typically form larger sheets and papillary units, whereas the sheets in (well differentiated and large-duct variants of) PDACs are typically associated with significantly more disorganization (\textit{drunken honeycombs}), nuclear contour irregularity, and chromatin clumping or hypochromasia.\textsuperscript{29}

Tumors with acinar differentiation (acinar cell carcinoma and mixed acinar cell-neuroendocrine carcinoma) may also resemble IOPN on FNAB, because they also have relatively monotonous nuclei with single, prominent nucleoli and abundant, granular cytoplasm in some cases.\textsuperscript{30,31} In some of our cases, this differential was given serious consideration. Acinar cell carcinomas also are often large, perhaps even larger than oncocytic IPMNs (average, 10 cm), and often exhibit cystic degeneration.\textsuperscript{32} More problematically, a subset of acinar carcinomas present with prominent intraductal growth, closely mimicking IPMN.\textsuperscript{30,31,33-36} However, acinar neoplasms are more mitotically active and necrotic than IOPNs. Intracellular and extracellular mucin, papillae, and cytoplasmic vacuoles/spaces also are not features of acinar cell carcinoma,\textsuperscript{37} which stain positively for pancreatic enzymes (trypsin, chymotrypsin, and lipase) and BCL10, markers not typically expressed by IOPNs.\textsuperscript{31,38} Mixed acinar cell-neuroendocrine carcinoma may exhibit cytology and immunohistochemistry similar to those of acinar cell carcinoma (in addition to expressing neuroendocrine markers), which helps with its distinction from IOPN.\textsuperscript{31}

Another close mimic is intraductal tubulopapillary neoplasm. This entity is defined by its tubular configuration, solid growth,\textsuperscript{6,39} and cytologic features (abundant cytoplasm and prominent nucleoli), which may be indistinguishable from those of IOPN. The close resemblance of intraductal tubulopapillary neoplasms to pancreatobiliary-type IPMNs and oncocytic intraductal neoplasms is not only an issue at the cytologic level but is also problematic in histologic sections. In fact, we have observed cases in which we were unable to clearly make this distinction (unpublished data).

Pancreatic neuroendocrine tumors may also exhibit striking oncocytic cytology,\textsuperscript{40-42} leading to misdiagnosis and potential confusion with IOPN.\textsuperscript{43} Tumor cells are typically plasmacytoid with granular cytoplasm and eccentric, round nuclei, which may contain prominent nucleoli. Their salt-and-pepper chromatin is unlike oncocytic IPMNs, and nucleoli (if present) are more central than in IOPNs. Oncocytic pancreatic neuroendocrine
tumors also express neuroendocrine markers (synaptophysin, chromogranin, and CD56), whereas IOPNs do not. Numerous tumors may metastasize to the pancreas, including hepatocellular and Hürthle cell carcinoma. These may be confused with IOPN and, despite being very uncommon in the pancreas, should be kept in mind.

**Conclusion**

The diagnosis of IOPN (oncocytic IPMN) is possible on cytologic samples because of its distinctive cytomorphic features. These include sheets and papilla of large oncocytic cells with dense, granular cytoplasm; large central nuclei; a high nuclear-to-cytoplasmic ratio; and large, typically peripherally located nucleoli that may or may not touch the nuclear membranes. It is important to recognize these characteristics, because these tumors differ biologically, prognostically, and molecularly from other IPMNs as well as PDACs, for which they are clinically mistaken. Despite their cytologic atypia, once resected, these tumors have a predominantly indolent clinical course. Accurate recognition on FNAB is paramount to the appropriate triage of patients and can prevent unnecessary chemoradiation, especially in those with noninvasive disease.

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**REFERENCES**


Figure 1.
(A) A hypercellular smear is composed of numerous sheets of epithelial cells (Diff-Quik stain). (B) Large, complex papillary units have an “antler-like” branching pattern similar to that observed in fibroadenoma of the breast (Papanicolaou stain). (C) Magenta-colored fibrovascular cores traversed some tumor cell clusters (Diff-Quik stain). (D) A hypercellular smear is composed of crowded sheets and singly dispersed oncocytic tumor cells (Diff-Quik stain).
Figure 2.
(A) A smear composed of oncocytic cells arranged in large, flat sheets with prominent nucleoli is shown (Diff-Quik stain). (B) Tumor cells have round to oval nuclei, prominent nucleoli, and abundant pink cytoplasmic granules, as highlighted in the *inset* (Papanicolaou stain). (C) Case 2 had large vesicular nuclei with slightly eccentric, prominent nucleoli and more nuclear contour irregularity than that observed in B (Papanicolaou stain). (D) Oncocytic features of the tumor cells are easily identifiable on this ThinPrep slide (Papanicolaou stain).
Figure 3.
Rigid, punched-out, intercellular spaces are visible on (A) Diff-Quik–stained and (B) Papanicolaou-stained smears and give a vaguely cribriform appearance to cell clusters. (C) Identical punched-out spaces are observed in this resected oncocytic intraductal papillary mucinous neoplasm composed of complex, branching, edematous papillae lined by oncocytic epithelium (H&E stain). (D) Intracytoplasmic pink mucin is observed in occasional tumor cells, as highlighted in the *inset* (Papanicolaou stain).
Figure 4.
Case 1 was an oncocytic intraductal papillary mucinous neoplasm that was misdiagnosed as pancreatic ductal adenocarcinoma on cytology. (A) Smears revealed crowded sheets of oncocytic cells (Diff-Quik stain). (B) Thick, colloid-like mucin was present and contained necrotic debris and clusters of atypical cells with prominent cytoplasmic vacuoles (Papanicolaou stain). (C) Occasional 3-dimensional groups with high nuclear-to-cytoplasmic ratio and irregular nuclear contours highly concerning for adenocarcinoma were present (Papanicolaou stain). (D) A corresponding cell block revealed numerous papillae with hyalinized fibrovascular cores lined by atypical oncocytic cells and no adenocarcinoma component (H&E stain).
Figure 5.
Case 5 was an oncocytic intraductal papillary mucinous neoplasm that had an invasive adenocarcinoma component identified on resection. (A) Smears reveal numerous 3-dimensional clusters of oncocytic cells with background necrotic debris (Diff-Quik stain). (B) There is marked nuclear pleomorphism and single-cell necrosis (Papanicolaou stain). (C) Prominent nucleoli and nuclear irregularity were striking in some areas (Papanicolaou stain). (D) A cell block revealed multiple, broad papillae with striking basophilic edema lined by oncocytic cells with occasional intranuclear inclusions (inset) and large, hyperchromatic nuclei (H&E stain).
Figure 6.
Case 5 was an oncocytic intraductal papillary mucinous neoplasm that had an invasive adenocarcinoma component identified on resection. (A) This wholemount slide reveals the intraductal location of a complex papillary neoplasm. (B) Papillae are lined by large oncocytic cells with (C) multiple, minute foci of microinvasive adenocarcinoma (see inset) and (D) lymph node metastasis (H&E stain).
<table>
<thead>
<tr>
<th>Case</th>
<th>Age, y</th>
<th>Sex</th>
<th>Location</th>
<th>Imaging Modality</th>
<th>Size on Imaging, cm</th>
<th>Additional Radiologic Findings</th>
<th>Radiologic Diagnosis</th>
<th>Cytologic Diagnosis</th>
<th>Histologic Diagnosis</th>
<th>Size of Invasion, cm</th>
<th>Follow-Up</th>
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<td>1</td>
<td>57</td>
<td>Man</td>
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<td>Mass communicates with pancreatic duct (7.5 mm)</td>
<td>Cystic and solid mass PDAC</td>
<td>PDAC with intraductal component</td>
<td>IOPN, 6.5 cm; negative margins</td>
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<td>ANED at 38 mo</td>
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<tr>
<td>2</td>
<td>56</td>
<td>Woman</td>
<td>Head</td>
<td>CT</td>
<td>5.6</td>
<td>Cystic mass in main and branch PDs with papillary projections and dilatation of PD to 3.3 cm</td>
<td>MD-IPMN with invasive component</td>
<td>IPMN vs cystic PDAC</td>
<td>IOPN, 8.7 cm, with minute focus of PDAC; margin positive for IPMN, LNs negative, confined to pancreas</td>
<td>0.3 with focal extravasated mucin</td>
<td>ANED at 15 mo</td>
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<tr>
<td>3</td>
<td>68</td>
<td>Woman</td>
<td>Head</td>
<td>CT</td>
<td>4.3</td>
<td>Cystic mass in pancreatic head with pancreatic duct dilatation to 7 mm</td>
<td>Cystic mass</td>
<td>IOPN, with high-grade atypia</td>
<td>IPMN, 3.3 cm, with high-grade dysplasia/carcinoma in situ; negative margins and LNs</td>
<td>None</td>
<td>LTF/U</td>
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<tr>
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<td>84</td>
<td>Man</td>
<td>Head</td>
<td>MRI</td>
<td>2.5</td>
<td>Dilated CBD 7 mm and pancreatic duct 6 mm; thickened septae and thick fluid observed</td>
<td>Macinous cyst: MCN vs IPMN</td>
<td>IOPN</td>
<td>IOPN, 2.2 cm, minute focus suspicious for PDAC; negative margins, LNs</td>
<td>0.1</td>
<td>Perioperative death, 23 d postsurgery</td>
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<tr>
<td>5</td>
<td>64</td>
<td>Woman</td>
<td>Body</td>
<td>MRI</td>
<td>3.7</td>
<td>Solid, circumscribed mass with central cystic component; PD dilated to 6 mm</td>
<td>PDAC</td>
<td>IOPN, with high-grade atypia, suspicious for invasion</td>
<td>IOPN, 4.5 cm, multifocal PDAC; negative margins, 5 of 17 LNs positive</td>
<td>&lt;2 cm aggregate microscopic measurement</td>
<td>ANED at 9 mo, receiving chemotherapy</td>
</tr>
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Abbreviations: ANED, alive with no evidence of disease; CBD, common bile duct; CT, computerized tomography scan; IOPN, intraductal oncocytic papillary neoplasm; LNs, lymph nodes; LTF/U, lost to follow-up; MCN, mucinous cystic neoplasm; MD-IPMN, main duct-intraductal papillary mucinous neoplasm; MRI, magnetic resonance imaging; PD, pancreatic duct; PDAC, pancreatic ductal adenocarcinoma.
## TABLE 2

Cytologic Findings in Oncocytic Intraductal Papillary Mucinous Neoplasms

<table>
<thead>
<tr>
<th>Cytologic Findings</th>
<th>Case</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>No/Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercellular</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>4/5 (80)</td>
</tr>
<tr>
<td>Extracellular mucin</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>2/5 (40)</td>
</tr>
<tr>
<td>Flat sheets</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>5/5 (100)</td>
</tr>
<tr>
<td>Single cells</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>2/5 (40)</td>
</tr>
<tr>
<td>3D groups</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>3/5 (60)</td>
</tr>
<tr>
<td>Papillary groups</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>5/5 (100)</td>
</tr>
<tr>
<td>Fibrovascular cores</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>4/5 (80)</td>
</tr>
<tr>
<td>Oncocytic cells</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>5/5 (100)</td>
</tr>
<tr>
<td>Nuclear irregularity</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>2/5 (40)</td>
</tr>
<tr>
<td>Anisonucleosis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>4/5 (80)</td>
</tr>
<tr>
<td>Prominent nucleoli</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>4/5 (80)</td>
</tr>
<tr>
<td>Eccentric nucleoli</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>5/5 (100)</td>
</tr>
<tr>
<td>Intranuclear inclusions</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>1/5 (20)</td>
</tr>
<tr>
<td>Mitotically active</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>0/5 (0)</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>3/5 (60)</td>
</tr>
<tr>
<td>Intercellular spaces</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>4/5 (80)</td>
</tr>
<tr>
<td>Cytoplasmic mucin</td>
<td>Yes, F</td>
<td>No</td>
<td>Yes</td>
<td>Y, F</td>
<td>Yes, F</td>
<td>Yes</td>
<td>4/5 (80)</td>
</tr>
</tbody>
</table>

Abbreviations: 3D, 3-dimensional; F, focal.
TABLE 3
Clinicopathologic Comparison of the Oncocytic Type of Intraductal Papillary Mucinous Neoplasm (IPMN) With Other IPMN Subtypes and Pancreatic Ductal Adenocarcinomas

<table>
<thead>
<tr>
<th>Variable</th>
<th>PDAC</th>
<th>IPMN, Gastric</th>
<th>IPMN, Intestinal</th>
<th>IPMN, Pancreatobiliary</th>
<th>IPMN, Oncocytic</th>
<th>Current Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative frequency on resection</td>
<td>65%</td>
<td>7%</td>
<td>2%</td>
<td>0.2%</td>
<td>0.4%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Age, y</td>
<td>66</td>
<td>66</td>
<td>66</td>
<td>Inadequate data</td>
<td>63%</td>
<td>66%</td>
</tr>
<tr>
<td>Sex: Men:women</td>
<td>1.1</td>
<td>0.76</td>
<td>1.1</td>
<td>Inadequate data</td>
<td>1.9%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Size, cm</td>
<td>3.6</td>
<td>2.7</td>
<td>4.5</td>
<td>3.3</td>
<td>6%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Imaging findings</td>
<td>Solid, hypodense, nonhomogeneous mass with infiltrative borders; a double-duct sign may be observed</td>
<td>Dilated branch duct(s) (80%); mural nodule in 30%</td>
<td>Dilated main duct (63%) ± branch ducts; mural nodule in 56%</td>
<td>Dilated main duct (49%) ± involvement of branch ducts; mural nodule in 57%</td>
<td>Large, solid or cystic, complex mass with circumscribed borders, ± branch (62%); main duct (38%) involvement; PET-avid because of high metabolic activity of oncocyctic cells; mural nodule in 100%</td>
<td>Cystic or cystic and solid mass with main duct and/or CBD dilatation</td>
</tr>
<tr>
<td>Histology</td>
<td>Infiltrative glands in abundant, desmoplastic stroma; glands with luminal necrosis adjacent to muscular arteries; variable N/C; prominent cytoplasmic vacuoles; PMI; LVI</td>
<td>Short, finger-like papillae or flattened mucinous epithelium identical to gastric foveolar epithelium; often accompanied by pyloric-like, basally oriented glands; more complex papilla when high grade</td>
<td>“Villous-intestinal” pattern revealing villi lined by pseudostratified, basophilic columnar epithelium with apical goblet-like mucin</td>
<td>Complex, arborizing papillae with inconspicuous fibrovascular cores, lined by low cuboidal epithelium, with high N/C, nuclear irregularity, and scant mucin production</td>
<td>Complex, arborizing papillae lined by 2-5 cell layers of oncocyctic cells; prominent intercellular spaces; scant cytoplasmic mucin; clean appearance with limited necrosis</td>
<td>Complex, arborizing papillae lined by 2-5 cell layers of oncocyctic cells; prominent intercellular spaces; scant cytoplasmic mucin; clean appearance with limited necrosis</td>
</tr>
<tr>
<td>Cytology</td>
<td>3D cell clusters with high N/C; 4-fold anisonucleosis, irregular nuclei, prominent nucleoli, cytoplasmic vacuoles, single-cell necrosis, and background necrosis</td>
<td>Abundant background colloid-like mucin ± oncocytic cells; mucinous epithelium in sheets ± papillae, low to intermediate N/C; U-shaped cytoplasmic mucin cup in superficial 1/3 of cells; mild anisonucleosis</td>
<td>Abundant background colloid-like mucin ± oncocytic cells; mucinous epithelium in sheets and papillae; intermediate to high N/C; columnar cells with pencillate, pseudostratified nuclei, goblet-like cytoplasmic mucin; moderate to marked anisonucleosis</td>
<td>Variable amount of background mucin; cells with high N/C, scant cytoplasmic mucin, 3D clusters, nuclear irregularity, hypochromasia/hyperchromasia, moderate to marked anisonucleosis</td>
<td>Scant background and intracytoplasmic mucin; variable amount of oncocytic cells; large oncocyotic cells in sheets ± papillae, with granular cytoplasm, large central nuclei, prominent slightly eccentric nucleoli, punched-out intercellular spaces; mild to moderate anisonucleosis</td>
<td>Scant background and intracytoplasmic mucin; variable amount of oncocytic cells; large oncocyotic cells in sheets ± papillae, with granular cytoplasm, large central nuclei, prominent slightly eccentric nucleoli, punched-out intercellular spaces; mild to moderate anisonucleosis</td>
</tr>
<tr>
<td>Frequency of high-grade</td>
<td>NA</td>
<td>Low</td>
<td>Low-moderate</td>
<td>High (present in all cases, by definition)</td>
<td>High (present in all cases, by definition)</td>
<td>High (present in all cases)</td>
</tr>
<tr>
<td>Variable</td>
<td>PDAC</td>
<td>IPMN, Gastric</td>
<td>IPMN, Intestinal</td>
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<td>IPMN, Oncocytic</td>
<td>Current Patients</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------------------------------------</td>
<td>---------------</td>
<td>------------------</td>
<td>------------------------</td>
<td>-----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Frequency of dysplasia</td>
<td>NA (100% invasive, by definition)</td>
<td>10</td>
<td>40</td>
<td>68</td>
<td>45 (but mostly microscopic)</td>
<td>60</td>
</tr>
<tr>
<td>Type of invasive carcinoma</td>
<td>Pancreatobiliary/tubular type</td>
<td>Tubular type</td>
<td>Colloid carcinoma (most); tubular type (rare)</td>
<td>Tubular type</td>
<td>Tubular type, oncocytic type</td>
<td>3 Tubular type (0.1, 0.3, and 2.0 cm)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Dismal (5-y survival, 4%)</td>
<td>Excellent if noninvasive (most cases), but dismal if invasive, because invasion is usually tubular type (in ~10%)</td>
<td>Excellent when noninvasive; for invasive disease, 5-y survival &gt;5%</td>
<td>Inadequate data; 5-y survival reportedly 55%</td>
<td>&gt;90% 5-y survival (even when invasive)</td>
<td>Limited (1 periop death; 1 LTFU; 3 ANED at 9, 15, and 38 mo)</td>
</tr>
</tbody>
</table>

Abbreviations: ±, with or without; 3D, 3-dimensional; ANED, alive with no evidence of disease; CBD, common bile duct; IOPN, IPMN-oncocytic type; LTFU, lost to follow-up; LVI, lymph-vascular invasion; N/C, nuclear-to-cytoplasmic ratio; NA, not applicable; PDAC, pancreatic ductal adenocarcinoma; periop, perioperative; PET, positron emission tomography; PNI, perineural invasion.