Intraductal Tubular Adenoma: A Case Report and Diagnostic Algorithm for Intraductal Pancreatic Lesions

Shivali Desai BS¹, Christine MG Schammel PhD²*, David P Schammel MD², A Michael Devane MD³, Steven D Trocha⁴

¹University of South Carolina School of Medicine Greenville, Greenville SC, USA
²Pathology Associates, Greenville SC, USA
³Department of Radiology, Prisma Health Upstate, Greenville SC, USA
⁴Department of Surgery, Prisma Health Upstate, Greenville SC, USA

*Correspondence should be addressed to Christine MG Schammel, Christine.schammel@prismahealth.org

Received date: August 29, 2022, Accepted date: October 11, 2022


Copyright: © 2022 Desai S, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Intraductal lesions of the pancreas are an increasingly recognized, radiologically detectable group of entities that require a systematic diagnostic approach to best define management given their variable prognoses. A case of isolated intraductal tubular adenoma (ITA) is reported with a comprehensive literature review; comparison of ITAs with intraductal papillary mucinous neoplasms (IPMNs) and intraductal tubular carcinomas (ITCs) is made with assessment of their distinctive imaging and histological findings and discussion of the evolution of these lesions' classifications with regards to the established literature. We designed and propose an algorithm for the evaluation of these intraductal lesions to create a systematic approach for the diagnosis and management of such lesions.

Keywords: Isolated intraductal tubular adenoma, Intraductal papillary mucinous neoplasms, ITA, IPMN, Diagnostic algorithm, Definitive diagnosis, Differentiation

Introduction

Intraductal lesions of the pancreas are an uncommon but increasingly recognized group of findings due to advances in imaging [1]. These radiologically detectable neoplasms are known to progress to or be associated with invasive adenocarcinoma and, as such, are classified as precursor lesions to pancreatic ductal adenocarcinoma [1]. Intraductal tubular adenomas (ITAs) are uncommon benign tumors within this classification that can be associated with intraductal papillary mucinous neoplasms (IPMNs), which have a variable malignant potential [2,3], and are distinct from intraductal tubular carcinomas (ITCs) [1], a rare cancer with a controversial prognosis [4]. These entities may be asymptomatic or present clinically with non-specific symptoms such as fatigue or abdominal discomfort [5,6]; dilated pancreatic ducts (main or branch) with a filling defect [1] is the non-specific radiologic evidence of these lesions requiring definitive histologic evaluation for accurate diagnosis, appropriate prognosis and optimal treatment. ITAs are often identified with IPMN in the main pancreatic duct or a branch duct [7], further complicating the prognosis and treatment of these combined lesions [1,8]; however, if the lesion is an isolated ITA, surveillance is warranted. Definitive differentiation of ITA, IPMN and ITC pre-operatively is essential to avoid surgery and its associated morbidity in cases of isolated ITA. Here we report a single case of isolated ITA diagnosed and treated at our institution and a comprehensive literature review with the purpose of advancing the diagnostic approach to best manage these rare lesions.

Case Report

An 83-year-old female with a history of CAD with CABG and stents, systolic CHF, HTN, and a distant 15 pack-year smoking history presented to the emergency department after a motor
vehicle accident. Contrast-enhanced abdominal CT to assess intraabdominal injury revealed multiple hypoattenuating lesions in the tail of the pancreas, the largest measuring 2.4 cm; due to streak artifact, evaluation was poor. A high density mass in the lower pole of the left kidney was also noted. A second non-contrast abdominal CT during hospitalization two days later noted the same findings. After receiving care for sustained orthopedic injuries, the patient presented to a surgical oncologist regarding the pancreatic finding. Physical exam was unremarkable. A subsequent abdominal CT with and without contrast approximately to further characterize the pancreatic lesions demonstrated a multi-septated cystic mass in the pancreatic tail (Figure 1a) measuring 4.6 x 3.9 cm with a component of soft tissue enhancement and an irregularly dilated distal pancreatic duct (Figure 1b). Differentials included pancreatic pseudocyst, cystic neoplasms or IPMN. Magnetic resonance cholangiopancreatography (MRCP; Figure 2) revealed a multiloculated cystic lesion in the pancreatic tail that measured 4.7 x 2.7 cm in the coronal view and 4.8 cm in the AP dimension; questionable internal solid components were noted but could not be thoroughly assessed due to lack of IV contrast. Mild to moderate irregular dilation of the adjacent main pancreatic duct (MPD) within the distal tail and body was also observed. The principal diagnosis was a main duct IPMN and thus, surgical intervention was recommended.

![Contrast enhanced CT](image1)

**Figure 1. Contrast enhanced CT a)** Axial image. Enhancing intra-ductal soft tissue nodularity within the pancreatic tail (white arrows). Dilated distal pancreatic duct (black arrow). **b)** Coronal image. Enhancing intra-ductal soft tissue nodularity (white arrow) within the pancreatic tail.
Intraoperative ultrasound was used to define transition of the MPD; a robotic distal (subtotal) pancreactectomy and splenectomy was completed. Pathology received the distal pancreas (11 x 3.5 x 2 cm) with an attached spleen. A 2.5 x 2 x 2 cm lesion 4.3 cm from the resection margin containing multiple papillary excrescences extending from the internal cystic lining and clear mucinous material was noted; while the splenic hilum was involved, no invasion of the splenic parenchyma was identified. A total of 28 lymph nodes were identified. Histologic analysis revealed closely packed tubular glands lined by columnar epithelial cells with foci of mild dysplastic change (Figure 3), consistent with chronic pancreatitis and low-grade intraductal tubular adenoma (ITA) of pyloric gland type. There was no evidence of increased mitotic rate or necrosis. The MPD was observed to be dilated at the resection margin with pyloric type epithelium without high-grade dysplasia or malignancy. All lymph nodes were negative for tumor. No immunohistochemical staining was necessary for definitive diagnosis.

Post-operative day three amylase was 34 IU/L indicating normal pancreatic function (range 25-125 IU/l); discharge with an amylase drain occurred post-operative day four.

Follow-up for ITA was unremarkable; the renal mass was evaluated by urology and due to the patient’s age and size of the mass, surveillance was recommended. Patient failed to follow up for any further outpatient visits for nearly two years with only intermittent medical attention through emergency departments. Recently, patient presented with increased leg swelling and was found to have acute chronic kidney disease. Non-contrast CT revealed no lesions in the remaining pancreas but did show an increase in size of the renal mass with multiple liver and lung lesions. The patient is being worked up for possible metastatic renal cell cancer.
Uncommon intraductal lesions of the pancreas, ITA, IPMN and ITC, present with similar clinical and radiological features, yet vary in prognoses, requiring precise histological diagnosis for appropriate management and follow up [1]. Controversy regarding the distinct classification of these lesions exists, with ITAs thought to be precursor lesions to ITCs; however, this has not been substantiated [8]. More commonly, due to histologic similarities, ITAs are considered a variant of gastric-type IPMN [1,8], with isolated ITA without associated IPMN rare, with fifteen cases noted in the literature (Table 1).

Isolated ITAs typically occur in middle aged patients (50-80 years) with our patient being the oldest reported (83 years; Table 1). Patients typically present asymptptomatically or with nonspecific symptoms such as loss of appetite or fatigue [1]; abdominal discomfort was noted, but to a lesser extent [5, 6]. Patients often have a history of chronic pancreatitis and physical exam is typically unremarkable [6,9,10].

Isolated ITAs are typically found in the head or body of the pancreas with only one previous case noted in the tail [11]; our case is the second such presentation in the tail. Imaging characteristically reveals a dilated main pancreatic duct with a filling defect and variable amounts of mucin [1]. All reported isolated ITAs, including our case, were found within the main pancreatic duct, which appears to be characteristic (Table 1).

Grossly, a well-demarcated, polypoid intraductal lesion that occludes the duct but does not invade the walls can be seen [1]; the tumor is often sessile but pedunculated lesions have been noted (Table 1). Microscopic analysis shows closely packed columnar to cuboidal tubular structures that resemble pyloric glands with the mucin producing cells displaying abundant clear cytoplasm and basally oriented nuclei [1]; goblet and endocrine cells [6,9,10] with mild to moderate dysplasia [1] and few mitotic figures [9,10] may also be present. Immunohistochemical (IHC) positivity for MUC5AC and MUC6 appear characteristic, along with mutations in GNAS, KRAS, and RNF43 [1,12,13]. In regard to our patient, gross
Table 1. Comprehensive literature review of isolated ITA*

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Cases</th>
<th>Age</th>
<th>Gender</th>
<th>Location</th>
<th>Size, mm</th>
<th>Procedure</th>
<th>IHC Results</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shahinian</td>
<td>1992</td>
<td>1</td>
<td>69</td>
<td>F</td>
<td>MD, head</td>
<td></td>
<td>Whipple with truncal vagotomy; cholecystectomy; partial gastrectomy</td>
<td></td>
<td>Uneventful postoperative course; unknown prognosis post-discharge</td>
</tr>
<tr>
<td>Bakotic</td>
<td>1999</td>
<td>1</td>
<td>69</td>
<td>F</td>
<td>MD, tail</td>
<td>9</td>
<td>Distal pancreatectomy/splenectomy</td>
<td>gastrin-, synaptophysin-, chromogranin A-, somatostatin-, desmin-</td>
<td>Alive and symptom free 5 years after surgery</td>
</tr>
<tr>
<td>Albores-Saavedra</td>
<td>2004</td>
<td>3 (only 2 new cases, see note)</td>
<td>63</td>
<td>M</td>
<td>MD, head</td>
<td>28</td>
<td>Whipple procedure</td>
<td>CK7+/CK20--; focal CEA linear reactivity along the apical cytoplasm but few displayed cytoplasmic CEA; chromogranin-, synaptophysin-, serotonin-, gastrin-, somatostatin-. Approximately 5-10% of cells were positive for MIB-1, p53--; DPC4-</td>
<td>Both alive and NED 2 years and 4 months, respectively, after surgical resection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70</td>
<td></td>
<td>F</td>
<td>MD, head</td>
<td>50</td>
<td>Whipple procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Note: The article described 3 cases; however, the first was the same case that was described by Bakotic, et al.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakayama</td>
<td>2005</td>
<td>4</td>
<td>50</td>
<td>M</td>
<td>MD, head</td>
<td>20</td>
<td>PPPD</td>
<td>M-GGMC-1++; MUC6++; MUC5AC++; gastric mucin--; MUC1--; and mostly negative (sporadic in cases 2 and 3) for MUC2 and SIMA. Pepsinogen II was positive in all but case 1, while none contained pepsinogen I. Chromogranin A was expressed in all tumors except case 4 but to a lesser degree. DPC4 expression was strongly seen in all 4 tumors. All were negative for DO7.</td>
<td>All alive at time of publication with NED at 3 to 10.5 years from time of surgical resection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70</td>
<td></td>
<td>F</td>
<td>MD, head</td>
<td>13</td>
<td>SPDP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>67</td>
<td></td>
<td>F</td>
<td>MD, head**</td>
<td>10</td>
<td>PPPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>79</td>
<td></td>
<td>F</td>
<td>MD, head</td>
<td>22</td>
<td>PPPD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Year</td>
<td>Case</td>
<td>Age (Range)</td>
<td>Gender</td>
<td>Location</td>
<td>Tumor Type</td>
<td>Size (mm)</td>
<td>Treatment</td>
<td>Outcome</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Chang</td>
<td>2014</td>
<td>7</td>
<td>47 to 74 (avg 58)</td>
<td>5M, 2F</td>
<td>MD with 4 in head and 3 in body</td>
<td>Note: These 7 cases were part of a larger case study that compared and contrasted cases of ITA with cases of IPMNs and ITPNs.</td>
<td>6-30</td>
<td></td>
<td>MUC5AC+; MUC1-; 3/7 MUC2+; p53-</td>
</tr>
<tr>
<td>Desai</td>
<td>2022</td>
<td>1</td>
<td>83</td>
<td>F</td>
<td>MD, tail</td>
<td></td>
<td>25</td>
<td>Robotic laparoscopic distal (subtotal) pancreatectomy/splenectomy</td>
<td>Alive with NED 3 years after surgical resection</td>
</tr>
</tbody>
</table>

*Cases in which ITA was noted to be associated with IPMN were excluded from this study. MD: Main Duct; ITA: Intraductal Tubular Adenoma; ITN: Intraductal Tubular Neoplasm; IPMN: Intraductal Papillary Mucinous Neoplasm; ITPN: Intraductal Tubulopapillary Neoplasm; PPPD: Pylorus-Preserving Pancreaticoduodenectomy; SPDP: Spleen-Preserving Distal Pancreatectomy; NED: No Evidence of Disease. **Tumor was located at the junction between Wirsung and Santorini ducts. Note: For size, maximum diameter of the tumor was indicated. A shaded gray box indicates that the report did not have the information recorded.
and histologic characteristics mirrored the aforementioned findings from the MPD; no increased mitotic rate, cytological atypia, or necrosis were identified.

Isolated ITAs have historically been mistaken for other intraductal lesions, specifically IPMNs and ITCs; however, there are several key differences. Isolated ITAs are found in the MPD (Table 1); IPMNs are often found in branch ducts [9,10]. While both ITA and IPMN note swelling of the major papilla and a wide-open orifice filled with mucus and a filling defect inside the dilated pancreatic duct on imaging, ITAs produce variable mucus and IPMNs produce abundant mucus [10]. Unlike the well-demarcated polypoid mass seen grossly with ITAs, IPMNs are papillary to granular or flat and diffuse [10]. Histologically, ITA and IPMN both display glands lined with cuboidal to columnar mucin-secreting cells with abundant cytoplasm and basally oriented nuclei [6] with a spectrum of cytological atypia, but IPMNs display papillary growth with abundant papillae with foci or tubular structure and an invasive component [9,10]. ITAs only have a gastric phenotype (pyloric gland type), while IPMNs display more diversity with gastric, intestinal or pancreatobiliary phenotypes [10]. While the ITA IHC profile is consistently positive for MUC5AC and MUC6, IPMN displays more variability, in accordance to the specific phenotype; interestingly, the IHC profile of ITAs and gastric type IPMNs are identical [1]. Importantly, ITAs are benign, but approximately 19% of IPMNs can develop into an invasive adenocarcinoma, with the intestinal and pancreatobiliary phenotypes more frequently associated with this progression [7,10]; however, some reports suggest that this incidence may be lower [2].

ITAs share significant morphological similarities to the gastric-type IPMN such that some have classified ITA as a variant of gastric-type IPMN, which is reflected in the 2010 WHO classification [1,7,8,14]. Evidence for this classification has been demonstrated in a single report identifying ITA within a gastric-type IPMN, suggesting a shared lineage [15]; it is estimated that fifty percent of ITAs coexist with an IPMN within the same or nearby duct [7]. These findings led to subclassification of isolated ITAs into type A, ITAs without associated IPMN (“classic ITA”), and type B, ITAs with associated gastric-type IPMN (“mixed ITA”) [7].

Differentiation of ITA and ITC can be completed on imaging, as ITCs exhibit a “mass-clogged” duct without significant mucus [1]. And, while histologically ITA and IPMN display glands lined with cuboidal to columnar mucin-secreting cells [6] with a spectrum of cytological atypia, ITC displays nodules of closely packed or fused glands that demonstrate a complex cribriform pattern resembling pancreatobiliary epithelium with uniform high-grade dysplasia and variable invasion [1]; goblet cells are absent and necrosis is present [1].

Determining the evolution of ITAs has proven difficult. ITAs have been suggested to be precursor lesions of ITCs [1] from a report identifying an ITC within an ITA [16]; however, mitotic rate and necrosis were not reported allowing for the differentiation of a true carcinoma from a rapidly proliferative ITA clone [7]. Another report suggested an intestinal, not pyloric, type of ITC exhibited focal transformation into intestinal ITC [17]; however, no pyloric type tubules were observed in the ITC component and the reported histological findings were similar to ITC [17]. IHC differences also suggest different biology as, while both ITA and ITC express MUC6, ITC expresses MUC5AC and ITC expresses MUC1. Likewise, molecular studies have also demonstrated the lack of relationship between ITAs and ITCs: ITAs and IPMNs have GNAS, KRAS, and RNF43 mutations, while ITCs exhibit PIK3CA mutations [1,12,13]. Further differentiation of ITA from ITC classified ITC as a type of intraductal tubulopapillary neoplasm (ITPN) [8,18], noting that ITAs are not similar to the precursor lesions of ITPNs [6].

Although ITA has histologically distinguishing characteristics, the most challenging issue is differentiating ITA from IPMN and ITC in the preoperative setting to provide the most appropriate treatment. CT is frequently the first imaging used to assess these lesions, given these lesions are often found incidentally to evaluate nonspecific symptoms. Yet, CT is limited in its evaluation of key features of pancreatic lesions beyond size assessment [19]. Endoscopic ultrasound (EUS) and MRCP could both demonstrate its filling defect, dilated duct, or in the presence of concerning or high-risk features, such as mural nodules and presence of solid components [19]. On the contrary, MRCP may be preferred when there is uncertainty of an intraductal lesion versus another lesion such as a pseudocyst [20]. In cases of ITAs and IPMNs, both contrast-enhanced EUS and MRCP show similar findings, while ITCs may be more easily distinguished [1]. EUS has been shown to accurately assess IPMNs in MD-IPMNs, BD-IPMNs, and mixed-type tumors [21]; contrast-enhanced EUS, specifically, has been shown to identify the malignant features of IPMNs [19,21]. When considering ITAs, contrast enhanced EUS or MRCP could both demonstrate its filling defect, dilated duct, and lack of malignant features. Nevertheless, there are limited cases in the literature to reliably differentiate between these lesions solely on imaging [1]. The ability of EUS to perform a biopsy is helpful to provide a definitive diagnosis [21].

Currently, histologic analysis appears to be the gold standard in the differentiation of these lesions making endoscopic biopsy the appropriate tool for pre-operative assessment to avoid unneeded surgery for ITAs and optimize management of IPMN and ITC. Sampling error is always a concern with biopsies as ITAs often can be found with associated gastric-type IPMN in approximately fifty percent of cases and IPMN may not be identified [7]; however, research has shown that the associated gastric-type IPMNs are low-grade lesions that typically do not progress into invasive carcinoma [7].
Additionally, while IPMNs of the intestinal and pancreatobiliary types have a greater malignant potential, there have been no reports of ITAs co-existing with these types of IPMNs [7]. Given these data, a diagnostic/treatment algorithm was developed which provides the steps necessary to assist with the specific diagnosis of intraductal pancreatic lesions. When reviewing the algorithm (Figure 4), a CT, preferably contrast-enhanced, would initially characterize these lesions as a hypoattenuating lesion or cystic mass within the pancreas with a dilated duct and filling defect. An MRCP, preferably contrast-enhanced, to better locate and characterize the lesion as intraductal and rule out cystic lesions should be completed. Finally, EUS, potentially contrast-enhanced if available, with biopsy should be performed to provide focused imaging to identify the presence of malignant features and to procure the specimen for histological analysis to include definitive microscopic
characterization and IHC profiles; indeterminant biopsies should be repeated. A diagnosis of ITA favors surveillance to avoid the morbidity associated with surgery. If biopsy were to show ITC or IPMN of intestinal or pancreatobiliary type, then surgical management can be more confidently pursued while following established NCCN guidelines.

Conclusion

Intraductal lesions of the pancreas have become increasingly recognized and require a thorough diagnostic approach to optimize management. ITAs, which are designated as gastric type and are deemed a variant of gastric type IPMNs, are a benign entity that occurs with or without an associated IPMN, likely of gastric type, in the same or nearby duct. ITAs have not been substantiated to be a precursor lesion to ITC or other malignant lesions. However, IPMNs, particularly of the intestinal and pancreatobiliary subtypes, have been shown to progress to invasive adenocarcinoma, thus warranting consideration of surgical resection. If specific intraductal lesions can be diagnosed preoperatively, then management can be individualized to the patient. Using the proposed diagnostic and treatment algorithm we present here, clinicians can opt for endoscopic ultrasound with biopsy to best characterize these lesions and provide more definitive diagnosis based in combination with imaging findings, histological analysis and IHC profiles with the goal of surveillance for ITA and gastric type IPMNs and surgical resection for ITCs and pancreatobiliary and intestinal IPMNs.

Conflicts of Interest

All authors report no conflicts of interest. Dr. Devane has been a paid speaker for Johnson and Johnson and is a consultant with Boston Scientific. Dr. Trocha has been a paid speaker for Johnson and Johnson and is a consultant with Boston Scientific.

Funding

No funding was received for this study.

Author Contribution

S Desai: data collection, initial manuscript; C Schammel: project oversight, edits; D Schammel: histology figures, legends, editing; AM Devane: imaging figures, legends, editing; S Trocha: conceptualization, project oversight, editing


