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Review Article

Intraductal tubular neoplasms of the pancreas: an overview☆

Adeline Chelliah, MBBCh, FRCPath, Sangeetha Kalimuthu, MBBCh, FRCPath, Runjan Chetty, MBBCh, FRCPath, FRCPC, DPhil *

Department of Pathology, Laboratory Medicine Program, University Health Network and University of Toronto, Toronto, Canada

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ABSTRACT

Intraductal lesions of the pancreas are an uncommon but increasingly recognized group of entities mainly because of advances in imaging technology. In the past, precise categorization and understanding of true pancreatic intraduct neoplasms were hampered not only by their relative rarity but also because of the plethora of terminology and criteria used in nomenclature and diagnosis. Although significant progress has been made in the characterization of some of these lesions, as exemplified by intraductal papillary mucinous neoplasms, understanding of the rare intraductal tubular adenoma (ITA) and intraduct tubular carcinoma (ITC) continues to evolve. By definition, these are a group of intraductal, radiologically detectable neoplasms that can progress to or be associated with invasive adenocarcinoma and, as such, are precursor lesions to pancreatic ductal adenocarcinoma. Their often shared clinical and radiological features make precise histological diagnosis essential for appropriate management and optimal outcome. We provide an overview of these neoplasms and highlight recent developments in the understanding of ITA and ITC which have led to ITA being considered a variant of gastric-type intraductal papillary mucinous neoplasms and ITC being encompassed within the intraductal tubulopapillary neoplasm category. We also emphasize the distinguishing histological features to aid diagnosis of these rare lesions.

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1. Overview of nomenclature and classification

Intraductal lesions of the main pancreatic duct and their immediate branches are uncommon but are increasingly recognized. This is attributable mainly to advances in modern diagnostic imaging technology [1,2].

In the past, precise categorization and understanding of true pancreatic intraduct neoplasms were hampered not only by their relative rarity but also because of the confusing, inconsistent terminology and diagnostic criteria. This was additionally complicated by primary pancreatic neoplasms with predominant or exclusive intraductal location/growth such as pancreatic ductal adenocarcinoma (PDAC) involving ducts (cancerization of ducts) and intraductal growth of solid tumors such as acinar cell carcinoma or pancreatic neuroendocrine tumors.

The best recognized of this group constituting bona fide pancreatic intraductal lesions is the intraductal papillary mucinous neoplasm (IPMN). Although IPMN is not the focus of this review, a brief note is included here for completeness. Although historical reports on "papillomatosis and cancer of the pancreatic ductal system" can be found in the German literature as far back as the 1930s [3], it was not until 1982 that Ohashi et al [4] delineated a subset of pancreatic intraductal tumors associated with diffuse dilatation of the main pancreatic duct and prominent mucin production. The 4 tumors in this series had a better prognosis than conventional PDAC, highlighting the importance of distinguishing them from other entities. Unfortunately, this lesion was reported under a variety of terms reflecting their different facets and association, including *mucin-producing tumour*, *mucinous duct ectasia*, *ductectatic mucinous cystadenoma/cystadenocarcinoma*, *papillary adenoma*, and *villous adenoma* among others. International consensus was achieved in the 1990s with the unification of this entity under the medical moniker *intraductal papillary mucinous neoplasm* (IPMN) introduced by Sessa et al [5].

Over time, additional variants of intraductal neoplasms were encountered demonstrating a more tubular or tubulopapillary growth pattern with little or no mucin [6–8]. This led to a widely used system, advocated by the Japan Pancreatic Society and American Registry of Pathology [9,10], dividing pancreatic intraductal tumors into IPMNs and so-called intraductal tubular neoplasms (ITNs). ITNs were further subdivided into intraductal tubular adenomas (ITAs) and intraductal tubular carcinomas (ITCs) based on the degree of epithelial atypia present. With this system, there was an implication that ITA was a precursor of ITC. However, this has not been borne out, as current evidence indicates that these 2 lesions have distinct morphological, immunohistochemical, and molecular features as will be discussed below.

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* Corresponding author at: Department of Pathology, 11th Floor, Eaton Wing, Toronto General Hospital, 200 Elizabeth St, Toronto, M5G 2C4, Ontario, Canada. Tel.: +1 416 340 5319.

E-mail address: runjan.chetty@gmail.com (R. Chetty).

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The current *WHO Classification of Tumours of the Digestive System* [11] defines intraductal neoplasms of the pancreas as macroscopic (cystic or mass-forming) epithelial neoplasms with ductal differentiation that characteristically grow primarily within the ductal system and categorizes them as IPMNs and intraductal tubulopapillary neoplasms (ITPNs), which were previously designated ITNs. In contrast to the Japan Pancreatic Society and American Registry of Pathology system, the WHO considers ITA as a variant of gastric-type IPMN and incorporates ITC in the ITPN category in light of their many similarities.

The differing, parallel systems used in the classification of these lesions not only are confusing but also preclude standardization of reporting and comparison of data. International consensus for one classification system is needed to facilitate progress in further understanding and characterization of these rare lesions. This is particularly important because intraductal neoplasms of the pancreas are accepted precursor lesions to PDAC and they can progress to, or be associated, with invasive adenocarcinoma. Worldwide, pancreatic cancer accounts for 4% of all cancers diagnosed but is the seventh most common cancer death, reflecting its notoriously poor prognosis [12]. Thus, early accurate identification and management of these precursor intraductal neoplasms are essential in the quest to improve pancreatic cancer outcomes.

The focus of this review is to highlight advances in the understanding of the clinicopathologic, radiologic, and molecular features of the less commonly encountered ITA and ITC, with a particular emphasis on their histology and distinguishing features.

2. Intraductal tubular adenoma (now considered a variant of gastric IPMN)

Intraductal tubular adenoma or ITA pyloric type of the pancreas was initially reported in 1992 by Shahinian et al [6] as a "tubular adenoma of the duct of Wirsung" followed in 1999 by Bakotic et al [7] using the term *pyloric gland adenoma of the pancreas*. It is a rare entity that is morphologically similar to the pyloric tubular/papillary adenoma occurring in the gallbladder. From the small number of cases reported in the literature, there does not appear to be a sex predilection and the lesion occurs in the fifth to seventh decades. Patients are asymptomatic or present with nonspecific symptoms such as loss of appetite or fatigue.

Radiological examination shows a dilated duct with a filling defect and varying amounts of mucin.

A polypoid intraductal lesion is seen macroscopically, often filling and occluding the lumen that may result in cystic dilation of the duct.

Microscopic evaluation reveals closely packed tubular or glandular structures that are highly reminiscent of pyloric glands (Fig. 1). Although the predominant architecture is tubular, occasional villiform or papillary areas may be seen. The lining epithelium is cuboidal to low columnar with maintenance of nuclear basal polarity (Fig. 1, inset). The nuclei are round to oval with small nucleoli. The cytoplasm can vary from eosinophilic to pale. The degree of cytological atypia is low in grade (Fig. 1, inset). Mitotic counts in the small numbers of cases evaluated have been reported to be as low as 1-5/10 high-power fields (HPFs) [13] and up to 10/10 HPFs [14]. Atypical forms are not identified. Necrosis is unusual and invasion is not seen. Scattered goblet cells and endocrine cells may be present. There is usually a sharp demarcation between the lesion and the adjacent, often cystically dilated, duct. Low-grade pancreatic intraepithelial neoplasia (PanIN) can be seen in surrounding small pancreatic ducts.

Changes secondary to torsion may be present, including cystic dilatation of glands, edema, and an exuberant fibroinflammatory response (Fig. 2A and B) [15]. This particular example of ITA was also associated with a gastric-type IPMN, a coexistence reported in at least 50% of ITA cases (Fig. 2A) [13,14,16–19]. In these cases, the ITA may mimic a mural nodule in an IPMN, which would raise more aggressive connotations. Awareness and careful examination of the imaging would prevent a misdiagnosis.

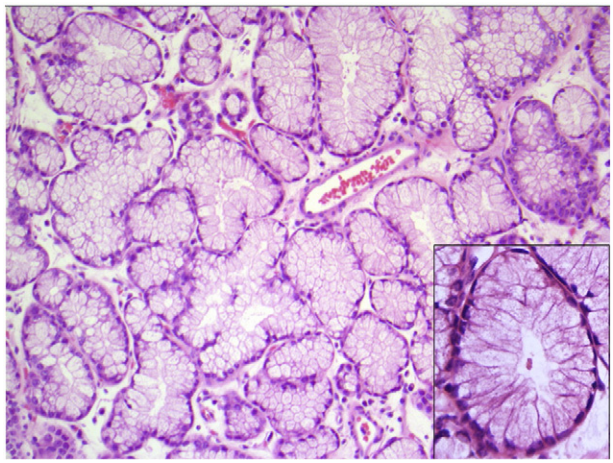

Fig. 1. Intraductal tubular adenoma comprising closely packed tubular/glandular structures resembling pyloric glands. The lining epithelial cells are columnar, with abundant clear apical mucin and basally orientated nuclei, which show low-grade cytological atypia (inset) (×100 magnification; hematoxylin and eosin [H&E]).

There is a great deal of morphological overlap noted between ITA and gastric-type IPMN, both of which are generally low-grade neoplasms with good prognosis. They have similar mucin expression profiles, that is, MUC6 and MUC5AC [20]. Significantly, like gastric-type IPMN, ITA pyloric type has been found to contain frequent mutations in *GNAS* and *KRAS* [21,22], which lend credence to the belief that they are a variant of gastric-type IPMN.

The 1 difference between the 2 tumors is location, in that ITA pyloric type tends to occur in Main pancreatic duct (MPD) whereas gastric-type IPMNs are mainly located in branch ducts. Hypotheses to explain this divergence include the possibility that ITA pyloric type may represent a localized form of gastric Intraductal papillary mucinous neoplasm (IPMN) in the MPD or that this variation may be related to the innate adaptability of the pancreaticobiliary lining epithelium [14].

3. Intraductal tubular carcinoma (included in the WHO ITPN group)

Because of their many shared features, ITCs are part of the ITPN group according to the WHO classification. They are very rare tumors, and clinical behavior has yet to be fully determined. From the limited data available, they appear to affect both sexes equally with a median age of 61 years [23]. Symptoms are nonspecific and include abdominal pain; vomiting; diabetes mellitus; weight loss; and, uncommonly, obstructive jaundice. Approximately 50% of tumors are located in the pancreatic head, whereas 30% show diffuse involvement of the pancreas [11].

Imaging studies reveal a "mass-clogged" duct without significant associated mucin. Grossly, a large, solid nodular mass is seen in dilated pancreatic ducts without prominent mucin.

Histologically, these intraduct tumors show uniform high-grade dysplasia and comprise nodules of closely packed or fused glands resulting in a complex cribriform pattern (Fig. 3A). The main architecture is tubular, but papillary or solid areas may also be appreciated. The lining epithelium is cuboidal with little cytoplasm and resembles pancreaticobiliary epithelium. There are nuclear enlargement, stratification, and overlap with prominence of the nucleoli (Fig. 3B). The number of mitoses encountered is extremely variable but generally amounts to >5/50 HPFs, and necrosis is frequently seen. Mucin is absent or scant, and goblet cells are not seen. Foci of calcification may be identified.

The invasive component can be difficult to discern because the neoplastic nodules lack a discrete peripheral rim. Features indicative of invasion are architectural complexity, irregular glands, detached single cells or small clusters of tumor cells, stranding of tumor cells into the adjacent parenchyma, and stromal desmoplasia (Fig. 3C and D). In view of

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