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Editorial

# Forerunner and Sap-Intra-Ductal Papillary Mucinous Neoplasm-Pancreas

**Anubha Bajaj***

Department of Histopathology, AB Diagnostics, New Delhi, India

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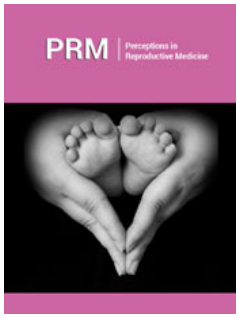


***Corresponding author:** Anubha Bajaj, Department of Histopathology, AB Diagnostics, New Delhi, India

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## Editorial

Intra-ductal papillary mucinous neoplasm emerges as a grossly discernible, non-invasive, cystic mucinous epithelial neoplasm arising from main pancreatic duct or branch ducts. The neoplasm manifests as a precursor lesion of pancreatic adenocarcinoma and commonly exemplifies >5 millimetre magnitude. Tumefaction is composed of diverse cellular subtypes demonstrating variable cytological and architectural atypia. Tumefaction is additionally classified as low grade lesion constituted of low grade or intermediate grade dysplasia, high grade lesion and neoplasm with an associated invasive carcinoma. The grossly discernible, cystic pancreatic neoplasm exceeding >5 millimetre magnitude is commonly confined to head of pancreas and demonstrates distinctive subtypes as intestinal, gastric, pancreaticobiliary or oncolytic. Comprehensive surgical resection is accompanied by >90% 5 year survival. Around one third (~33%) of neoplasms delineate an associated invasive carcinoma. Low grade to intermediate grade dysplasia was erstwhile nomenclated as intra-ductal papillary mucinous adenoma whereas high grade dysplasia was previously denominated as intra-ductal papillary mucinous carcinoma, non-invasive. Lesions with an associated invasive carcinoma were designated as intra-ductal papillary mucinous carcinoma, invasive variant. Additional terminologies erstwhile adopted to describe the neoplasm are mucin producing tumour, mucinous duct ectasia, duct-ecstatic mucinous cystadenoma/cystadenocarcinoma, villous adenoma or papillary adenoma/carcinoma.

Intra-ductal papillary mucinous neoplasm commonly arises within sixth decade to seventh decade. A male predominance is observed [1,2]. Intra-ductal papillary mucinous neoplasm incriminating pancreatic main duct commonly arises within head of pancreas and ~33% lesions are confined to body or tail of pancreas. Intra-ductal papillary mucinous neoplasm occurring within branch duct generally implicates head of pancreas or uncinate process. Multiple, distinctive lesions may appear in ~33% subjects [1,2]. Non-invasive intra-ductal papillary mucinous neoplasm or tumours with associated invasive carcinoma demonstrate genomic mutations within KRAS, GNAS and RNF43 genes, in decreasing order of frequency. GNAS chromosomal mutation is commonly associated with intra-ductal papillary mucinous neoplasm harbouring invasive colloid carcinoma. KRAS genetic mutation frequently accompanies lesions which harbour invasive tubular or ductal adenocarcinoma [1,2]. Enhancing grades of cellular or nuclear dysplasia delineate increasing chromosomal mutations within KRAS, TP53 or CDKN2A (p16) genes. Besides, hyper-methylation and decimated values of BRG1 protein are exemplified. Loss of programmed cell death 4 (PDCD4) and expression of CD24 is associated with cellular proliferation and tumour progression. Aspirated cyst fluid enunciates chromosomal mutations within KRAS2 and GNAS genes [1,2]. Of obscure aetiology, cigarette smoking may induce intra-ductal papillary mucinous neoplasm. The condition may be associated with Peutz-Jeghers syndrome and Familial Adenomatous Polyposis (FAP) [1,2].

Main duct intra-ductal papillary mucinous neoplasm enunciates high grade dysplasia (~60%) and an associated invasive carcinoma (~45%). Branch duct intra-ductal papillary mucinous neoplasm is predominantly a low grade lesion. However, high grade dysplasia (~25%) and associated invasive carcinoma (~20%) may ensue [1,2]. Invasive carcinoma

associated with intra-ductal papillary mucinous neoplasm is comprised of ~Tubular (ductal) adenocarcinoma is encountered within ~50% instances and demonstrates a slightly superior prognosis, in contrast to non-intra-ductal papillary mucinous neoplasm associated pancreatic ductal adenocarcinoma. ~Colloid carcinoma is enunciated within ~50% instances and exhibits superior prognosis as compared to pancreatic ductal adenocarcinoma [1,2]. Upon gross examination, incrimination of main duct exemplifies a diffusely dilated, tortuous and irregular duct permeated with mucin. Typically, the neoplasm commences within head of pancreas and progresses along path of main duct. Entire pancreas or major or minor papillae may be implicated with consequent extrusion of mucin from ampulla. Uninvolved pancreas appears as a pale, firm organ which is afflicted by concurrent extensive chronic obstructive pancreatitis. Implication of branch duct frequently commences within uncinate process of pancreas and configures multi-cystic, grape-like articulations or cystic dilatation of ducts permeated with tenacious mucin. Commonly, cyst wall is attenuated, flattened or layered with papillae. Cysts appear demarcated from normal, uninvolved pancreas, thereby indicating segregated cysts. Multi-centric lesions appear in ~40% instances [3,4]. Extensive tissue sampling or complete resection of cyst for microscopic evaluation is imperative for excluding an associated invasive carcinoma. Incipient intra-ductal papillary mucinous neoplasm is a terminology adopted for lesions which exemplify a duct diameter varying from 0.5 centimetre to 1.0 centimetre [3,4].

Upon frozen section, typically surgical margin status of pancreatic resection specimen requires evaluation in order to exclude intra-ductal papillary mucinous neoplasm. Additional evaluation of surgical margins is necessitated to exclude concurrent invasive carcinoma or possible emergence of high grade dysplasia. Characteristically, low grade dysplasia does not require additional resection and the lesion may mandate distinction between pancreatic intraepithelial neoplasia (Pain) or intra-ductal papillary mucinous neoplasm [3,4]. Cytological aspirate is composed of disordered mucinous epithelial cell clusters with overlapping nuclei and variable cytological atypia. Upon cytological examination, distinction of intra-ductal papillary mucinous neoplasm from mucinous cystic neoplasm or neoplastic mucinous cyst appears challenging. Also, distinction of low grade mucinous neoplasm from gastrointestinal tract mucosal contaminant, especially gastric mucosa can be challenging [3,4]. Upon microscopy, mucin producing epithelial cells delineate variable degree of cellular and nuclear dysplasia.

a) Low grade dysplasia characteristically depicts flattened epithelial layer with basal nuclei devoid of significant cellular and nuclear pleomorphism.

b) Intermediate dysplasia displays features between low grade and high grade dysplasia. Contemporary classification of low grade dysplasia is inclusive of low grade and intermediate dysplasia.

c) High grade dysplasia characteristically depicts complex architectural configurations as irregular, branching epithelial layer or cribriform pattern along with features such as loss of nuclear polarity, innumerable hyperchromatic nuclei and nuclear irregularities [3,4].

Epithelial cells exhibit variable differentiation and are sub classified into

i. intestinal subtype

ii. gastric subtype

iii. pancreaticobiliary subtype.

An oncolytic epithelial cell layer is indicative of intra-ductal oncolytic papillary neoplasm [3,4]. Intra-ductal papillary mucinous neoplasm may be associated with pancreatic intraepithelial neoplasia (PanIN) or chronic pancreatitis. Circumscribing ovarian type stroma is generally absent (Figure 1 & 2). Occurrence or absence of invasive carcinoma requires assessment, a feature which manifests as a significant prognostic factor.

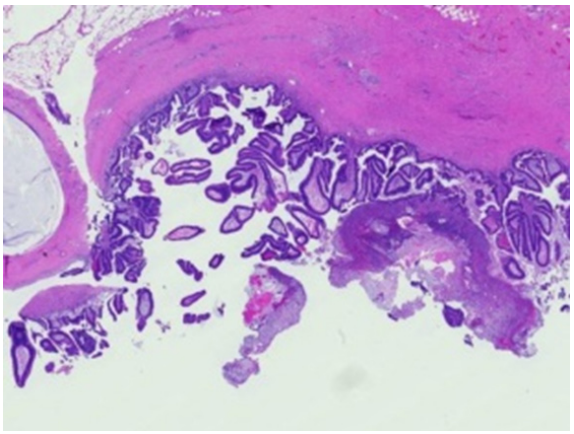

**Figure 1:** Intra-ductal papillary mucinous neoplasm depicting papillary projections layered with mucin producing columnar epithelial cells with loss of polarity, stratification, hyperchromatic nuclei and abundant intraluminal mucin surrounded by dense stroma.

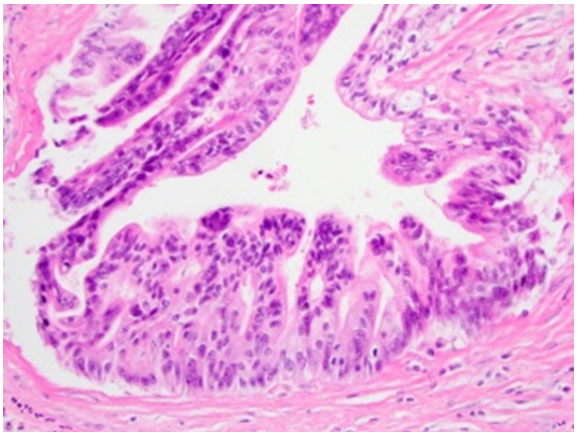

**Figure 2:** Intra-ductal papillary mucinous neoplasm delineating papillary projections coated with mucin secreting columnar epithelial cells with stratification, hyperchromatic nuclei, loss of polarity and minimal intraluminal mucin with dense circumscribing stroma.

Tumour invasion exemplifies a variable staining pattern of MUC1 or MUC2 upon immunohistochemistry [3,4]. Intra-epithelial papillary mucinous neoplasm exhibits cogent variants denominated as

A. Gastric type lesion is comprised of cells which resemble gastric foveolae. Foci of intestinal metaplasia may appear, especially concurrent with low grade dysplasia and branch duct intra-ductal papillary mucinous neoplasm. Typically, associated invasive carcinoma configures as ductal or tubular adenocarcinoma.

B. Intestinal type lesion is constituted of tall columnar epithelial cells, reminiscent of intestinal villous adenomas. Generally, low grade or high grade dysplasia and main duct intra-ductal papillary mucinous neoplasm are enunciated. Typically, associated invasive carcinoma manifests as mucinous or colloid carcinoma.

C. Pancreaticobiliary type intra-ductal papillary mucinous neoplasm is comprised of complex, thin, branching papillae simulating cholangiopapillary neoplasms.

Layering epithelium is composed of cuboidal cells imbued with prominent nucleoli. Generally, high grade dysplasia and main duct intra-ductal papillary mucinous neoplasm concurs with the variant. Typically, associated invasive carcinoma manifests as ductal or tubular adenocarcinoma [3,4]. Intra-ductal papillary mucinous neoplasm is immune reactive to general ductal markers as CK7, CK19, CA19-9, B72.3 and Carcinoembryonic Antigen (CEA) (Table 1). Besides, Mucin Glycoprotein (MUC) as MUC5AC+, MUC2+, CDX2+, MUC1+or MUC6+ may appear immune reactive. Intra-ductal papillary mucinous neoplasm is immune non-reactive to MUC1-, MUC2- [5,6]. Intra-ductal papillary mucinous neoplasm requires segregation from tumours such as intra-ductal oncolytic papillary neoplasm, intra-ductal tubulopapillary neoplasm, mucinous cystic neoplasm, pancreatic intraepithelial neoplasia (PanIN), simple mucinous cyst, retention cyst, pancreatic pseudocyst, serous cyst tumour or solid pseudo-papillary neoplasm. Intra-ductal papillary mucinous neoplasm confined to main duct can be appropriately treated with cogent surgical resection. Surgical intervention is indicated with occurrence of hyperbilirubinemia, mural nodules or main pancreatic duct diameter exceeding >10 millimetres [5,6].

**Table 1:** Differential diagnosis and morphology of pseudo-intra-ductal papillary mucinous neoplasm [2,3].

| Neoplasm | Morphology |
|---|---|
| Retention cyst (secondary duct ectasia) | Round, unilocular, smooth lining, open lumina, regular contours. Absent papillary structures or classical cell type |
| Large duct pancreatic ductal adenocarcinoma | Irregularly distributed large ducts with jagged edges, bland columnar mucinous cell layer. Variable papillomatosis |
| Simple mucinous cyst | Smooth internal lining of simple mucinous cells with occasional folding and atypia. Florid papilla formation absent. |
| Congenital cyst | Band of muscle coat, variable epithelia(respiratory) and accessory mucus glands |
| Para-duodenal wall cyst of PDP | Partially lined with epithelium, hyper-cellular reactive tissue with stromal deposition of acinar secretions along with inflammatory/ fibroblastic reaction |
| Conventional pseudocyst | Partly haemorrhagic & necrotic. Cyst wall composed of granulation tissue & fibro-inflammatory elements. Carcinoma cells invade and partly line inner layer of fibro-inflammatory cyst wall |
| Necrosis within tumour | Acellular hyalinised material with hyalinised, pauci-cellular cyst wall stroma along with carcinoma cells OR hyper-cellular inflammatory stroma within cyst wall. |

a) Branch duct intra-ductal papillary mucinous neoplasm can be subjected to surgical resection in Symptomatic instances.

b) Lesions with mural nodule ≥5 millimetre magnitude

c) Suspicious or malignant cells discernible upon cytological examination

d) Occurrence of obstructive jaundice

e) Main pancreatic duct diameter ≥10 millimetres. Intra-ductal papillary mucinous neoplasm devoid of an associated invasive carcinoma exhibits >90% proportionate 5 year survival. Neoplasms associated with an invasive carcinoma delineate adverse prognostic outcomes with proportionate mortality of ~50% [5,6].

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