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Pathophysiology, Incidence and Implications in Intraductal Papillary Mucinous Neoplasia of the Pancreas

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Introduction

Intraductal papillary mucinous neoplasms (IPMN) are uncommon tumors arising from the main pancreatic duct, branching pancreatic ducts, or both.

The "overall incidence of invasive carcinoma associated with resected IPMN has been reported to be 20-40%" (Mohri et al., 2011). Due to their malignant potential, these lesions, along with mucinous cystic neoplasms (MCN), are considered more worrisome, and often require surgical resection (Gallucci, Langellotto, De Ritis, & Uomo, 2012).

Even after removal of a primary lesion, patients remain under surveillance to monitor for recurrence, the rate of which is approximately 6 % (Gallucci et al., 2012), and patients with main duct IPMN are at a higher risk for developing pancreatic, gastric and colon adenocarcinoma over their lifetimes (Sheth, Howell & Kent, 2014).

While both main duct and side branch lesions are considered pre-malignant, management of IPMN has not been well-established (Mohri et al., 2011) and ranges from watchful waiting to surgical resection, depending upon the suspicion of malignancy, the operation required and the relative risk to the patient. A lower threshold for surgical resection is present for main duct IPMNs, as they have a higher risk of associated malignancy (Sahora & Castillo, 2014).

The incidence of pancreatic adenocarcinoma arising from IPMN has been well documented (Mohri et al., 2011). This poster discusses one such case. The patient's IPMN was initially discovered incidentally, during evaluation of an unrelated medical diagnosis.

As practitioners, it is important to be able to recognize IPMN as pre-malignant lesions and to act quickly to identify patients requiring further work-up. Since the prognosis of pancreatic adenocarcinoma is dismal, the early identification and treatment of IPMN, or pre-malignant lesions is imperative to improve outcomes (Mohri et al., 2011).

Case Presentation

The patient is a 51 year-old female who was noted to have multiple liver lesions at the time of imaging for her cholecystectomy several years ago. She was under surveillance for these liver lesions, which were felt to be focal nodular hyperplasia (FNH).

Surveillance imaging for her FNH noted a small, cystic lesion in the body of the pancreas measuring 0.6 centimeters. No follow up was done for this lesion.

In 2014 surveillance imaging, the patient's pancreatic cyst had increased in size to one centimeter and new pancreatic duct dilation and irregularity was described, as well as an appearance of chronic pancreatitis. Mild symptoms were present at this time, including abdominal cramping and bloating. No jaundice, weight loss or fatigue were reported.

She underwent an endoscopic ultrasound at this time, which demonstrated no significant abnormality in the pancreas. An abrupt change in the distal body and tail, distal to a focal calcification was described. This was suggestive of inflammation. Cysts measuring as large as 12 mm were noted, and fine needle aspiration was performed. The fluid was thin and blood-tinged.

Cytology results demonstrated no evidence of malignancy or mucin, and cyst fluid analysis for amylase and CEA were unable to be performed due to an inadequate amount of fluid.

The patient was seen in surgical consultation and elected to undergo the recommended surgical resection via distal pancreatectomy with splenectomy.

Final pathology revealed a 1.5 centimeter pancreatic tumor positive for moderately differentiated pancreatic ductal adenocarcinoma arising in intraductal pancreatic mucinous neoplasm with high-grade dysplasia involving the main duct and branches (mixed type). Of the 14 lymph nodes that were evaluated, zero were positive for adenocarcinoma.

Endoscopic Ultrasound often shows mucin arising from the main pancreatic duct, giving a "fish eye" appearance.



Courtesy of Mark Bloomston, MD

Margins were negative. The final staging was T1N0 (stage IA). The patient was referred to medical oncology and chemotherapy was recommended.

Signs & Symptoms

Patients with main duct and side branch IPMNs are often asymptomatic. Symptoms can include, abdominal discomfort and/or distress, vomiting, back pain, or signs of chronic pancreatitis (Grützmann, Post, Saeger, & Niedergethmann, 2011). Though uncommon, IPMN can cause mild acute pancreatitis (Jang et al., 2013). Symptoms predictive of malignancy include jaundice, weight loss or diabetes (Gallucci et al., 2012).

Radiographic evidence of IPMN includes the presence of a cystic lesion with a dilated main duct and evidence of communication between the cyst and the duct. MRI is more sensitive for detecting a mural nodule, which is considered a "strong predictive factor for malignancy" (Uehara et al., 2011).

Signs of IPMN on endoscopic ultrasonography include the presence of papillary growth in the ducts of the pancreas, communication between the cyst and the duct (either main or branch), and/or a clearly dilated main duct (Grützmann et al., 2011) with or without the presence of mucin within the duct. (Gallucci et al., 2012). Presence of mucin in the duct can have the classic "fish eye" appearance. Fine needle aspiration often demonstrates atypical cells or mucin, and laboratory evaluation of CEA levels greater than 2500 ng/mL are considered diagnostic. (Grützmann et al., 2011).

Pathophysiology of IPMN

IPMNs arise from the pancreatic ductal epithelium. The columnar epithelial tumor cells secrete mucin, leading to the dilation of the pancreatic duct and the associated symptoms of abdominal pain and pancreatitis. Intraductal papillary growth is also present. Cellular changes within the IPMN can vary from slight mucinous hyperplasia to invasive adenocarcinoma (Capurso et al., 2013). The cause of the development of IPMN is not fully understood, though they have been linked to several molecular changes.



The cystic structure in the distal pancreas appears to arise from the main pancreatic duct.

Courtesy of Mark Bloomston, MD

Possible Molecular Abnormalities in IPMN

- K-ras: Responsible for normal tissue signaling, K-ras is a protein that binds to GTP and referees signal transduction. Mutations in K-ras is present in up to 65% of IPMNs.
- CDKN2a: Mutations in this tumor suppressor gene have been associated with IPMN.
- Ring finger protein 43: This protein plays a role in suppressing mucus producing neoplasia of the pancreas. Mutations that inactivate this gene have been associated with IPMN.
- SMAD4: Intracellular proteins that code and transcribe extracellular signals in the nucleus. Expression of SMAD4 is present in most IPMNs.
- STK11: This gene, which acts as a tumor suppressor, is mutated in patients with Peutz-Jeghers syndrome. A subset of these patients have a higher risk of both IPMN and pancreatic cancer.
- MUC: These mucin mRNA, particularly MUC 1,2, and 5 are highly expressed in approximately 86% of IPMN. MUC1 and MUC2 are associated with malignancy.
- Promoter sequence hypermethylation: This process can cause gene silencing. Hypermethylation of tumor suppressor genes has been seen in patients with IPMN with greater degrees of dysplasia or even cancer.

(Sheth, Howell & Kent, 2014)

Implications for Nursing Care

As advanced practice nurses, it is important to consider incidental imaging findings and their clinical significance. In the case of incidental pancreatic findings, referral to pancreatologists or surgical oncologists is critical, as early detection of premalignant lesions will lead to increases in survival for many patients. Attention to vague symptoms, such as persistent abdominal complaints should be followed closely and IPMN should be in the differential diagnosis, especially when other causes have been ruled out.

Additional consideration should also be given to patients with a history of IPMN. Given their overall increased risk of both colon and gastric cancer, routine screenings, including upper and lower endoscopy, should be considered for these patients, though they may not be the recommended age for such testing.

Conclusion

IPMNs are precursors to invasive pancreatic adenocarcinoma. Recognizing their clinical significance is essential in practice and educating patients about their implication is a responsibility of the practitioner. Management of these premalignant lesions varies greatly depending upon subtype, patient age, comorbidities and morbidity of required surgery. Close surveillance with MRI and a multidisciplinary approach may be the preferred management for some patients, particularly those without suspicious findings (Roch et al., 2014).

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