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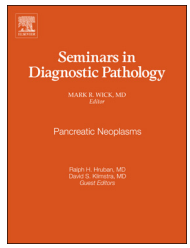

Mucinous cystic neoplasms of the pancreas: Update on the surgical pathology and molecular genetics

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ABSTRACT

Mucinous cystic neoplasms (MCNs) of the pancreas are primary pancreatic cyst-forming neoplasms that can be a precursor to invasive adenocarcinoma of the pancreas. MCNs occur almost exclusively in the distal pancreas of middle-aged women. MCNs typically show a "cyst-in-cyst" pattern of growth and are well encapsulated by a thick fibrous wall. MCNs are composed of mucin-producing neoplastic epithelial cells and "ovarian-type" subepithelial stroma. The epithelium is dysplastic and the grade can range from low to high grade; some MCNs have an associated invasive carcinoma. It is this associated invasive carcinoma that determines prognosis. MCNs harbor several characteristic genetic and epigenetic alterations, some of which are shared with conventional invasive pancreatic ductal adenocarcinoma. Furthermore, several studies reveal characteristic patterns of gene expression in the ovarian-type stroma that suggest steroidogenesis in the ovarian-type stroma. Better knowledge of the molecular alterations could help in the management of patients with this type of precursor of invasive carcinoma.

Introduction

Cystic lesions of the pancreas are increasingly being recognized with improvements in diagnostic imaging. Many of them are non-neoplastic benign cysts such as retention cysts and pseudocysts. Cystic neoplasms, including mucinous cystic neoplasms, are a minority of the cystic lesions of the pancreas.[1]

Mucinous cystic neoplasm (MCN) of the pancreas is one of the three most common primary cyst-forming neoplasms of the pancreas. These include intraductal papillary mucinous neoplasm (IPMN), serous cystic neoplasm (SCN), and MCN.[1,2] In 1978, Compagno and Oertel[3] clarified the distinction between serous and mucin-producing cystic neoplasms. In 1982, Ohashi et al.[4] first described "mucous secreting pancreatic cancer," a lesion we now call an IPMN. Despite these advances in our understanding, through most of the 1990s, the distinction between MCNs and branch-duct IPMNs was unclear and controversial because IPMNs were thought to be neoplasms mainly arising in the main pancreatic duct. Today IPMN is defined as an intraductal grossly visible (typically >10 mm) epithelial neoplasm of mucin-producing cells, arising in the main pancreatic duct (MPD) or its branches.[5] MCNs are defined as having two components, mucin-producing neoplastic epithelial cells that line cysts and a characteristic non-neoplastic "ovarian-type" subepithelial stroma.[6] Communication between the cyst locules and pancreatic ductal system is usually not observed in MCN.[6]

From another point of view, MCN is one of the three precursors of invasive adenocarcinoma of the pancreas: pancreatic intraepithelial neoplasia (PanIN), IPMN, and MCN.[2,7] Many molecular abnormalities found in PanINs

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and/or IPMNs are common in infiltrating ductal adenocarcinoma of the pancreas.[7–9] Although the reported genetic and epigenetic alterations in MCNs are much less numerous than those in ductal adenocarcinoma and other precursor lesions, recent technologies including oligonucleotide gene expression analyses (so-called "gene chip") and whole-exome sequencing revealed that MCNs also harbor several molecular abnormalities in common with invasive ductal adenocarcinoma, firmly establishing MCNs as bona fide precursor lesions.

In this review, we update the pathologic and molecular characteristics of MCN, with emphasis on diagnostic and clinical applications.

Clinical features

MCNs occur almost exclusively in the distal pancreas. The vast majority occur in women, with an average age at diagnosis of 40–50 years.[6,10–13] A couple of decades ago, patients with MCN typically presented with abdominal discomfort or epigastric pain due to enlargement of the neoplasm; however, more recently, with the increased use of imaging, many of the patients are asymptomatic and are incidentally diagnosed on abdominal imaging for another indication.

Patient prognosis after surgical resection is excellent if the neoplasm is non-invasive or if invasive carcinoma is confined to the ovarian-type stroma of the septa.[13–16] Identifying an associated invasive carcinoma is therefore critical. Malignancy is associated with the presence of mural nodules on imaging, lesion size (>6 cm)[14] and cyst wall calcification.[12] Even if an associated invasive carcinoma is present in an MCN, the prognosis of the patients after resection is better than that of patients with conventional invasive ductal adenocarcinoma not arising in an MCN; the 5-year survival rate of the MCN patients with an associated invasive carcinoma is up to 50%.[14] It is therefore important to detect, diagnose, and resect MCNs before they progress to an invasive carcinoma. At present we are not able to identify those MCNs that will progress to invasive cancer; all MCNs are therefore recommended to be resected regardless of size.[17]

Pathology of MCNs

Gross

MCNs usually form large, mean 6.5 cm in diameter, multilocular cystic masses in the tail of the pancreas; however, smaller lesions are increasingly being detected with the increasing quality and use of imaging. MCNs typically show a "cyst-in-cyst" pattern of growth and are well encapsulated by thick fibrous wall (Fig. 1). The cysts contain abundant mucus and sometimes some locules contain cloudy brown fluid or necrotic tissue, which suggests no communication among the cysts. The cysts typically do not communicate with the pancreatic duct system, though MCN can be sometimes communicate with the pancreatic duct system on ERCP,[15] and there is a case report of an MCN of the main pancreatic duct.[18]

Histology

The neoplastic epithelium lining the internal surface of the cyst wall can be flat or papillary (Fig. 2). The epithelial component consists of mucin-containing columnar cells with varying degrees of architectural and cytological atypia. MCNs are classified as MCN with low-grade, intermediate-grade, and high-grade dysplasia (conceptually the same as carcinomas *in-situ*), based on the most severely dysplastic focus identified (Fig. 2B–D). These various degrees of dysplastic epithelium often coexist within the same neoplasm as some locules can have low-grade dysplasia while others in the same neoplasm can have high-grade dysplasia. It is therefore absolutely critical that MCNs are extensively, if not

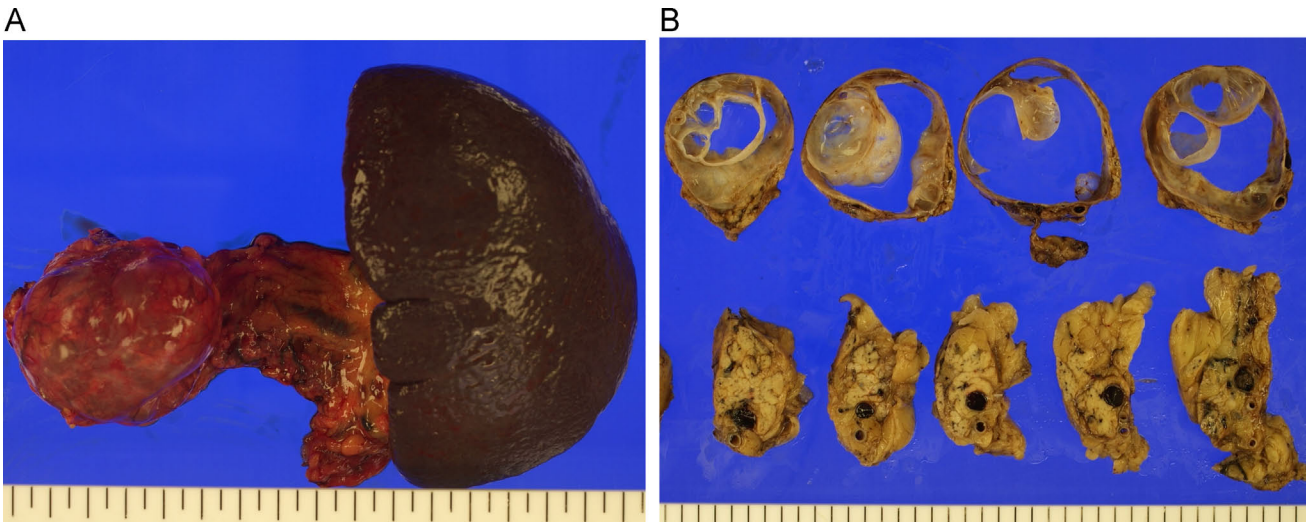

Fig. 1 – Gross appearance of the mucinous cystic neoplasms (MCNs). (A) A distal pancreatectomy and splenectomy. A cystic tumor is located in the body of the pancreas. (B) Cut surfaces of the MCN revealing the typical multiloculated and cyst-in-cyst appearance.