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Mucinous Cystic Neoplasms

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Abstract Mucinous cystic neoplasms of the pancreas are uncommon tumors of the pancreas that occur predominantly in middle-aged women and almost exclusively in the body and tail of the pancreas. They are lined by a mucinous epithelium that can exhibit varying grades of dysplasia and are surrounded by a characteristic ovarian-like stroma. Surgery is the treatment of choice, and prognosis is excellent in the absence of invasive carcinoma.

Keywords Mucinous cystic neoplasm · Ovarian stroma · Intraductal papillary mucinous neoplasm

Introduction

The initial description of mucinous cystic neoplasms (MCN) as a distinct entity affecting the pancreas was made by Compagno and Oertel in 1978.[1] They described them as large, septated, thick-walled cysts, filled with mucoid and occasionally hemorrhagic material, and occurring almost exclusively in the pancreatic body and tail of middle-aged women. The cysts were lined by an epithelium composed of tall mucin-secreting cells with various degrees of atypia. They also noted the presence of a dense cellular ovarian-type stroma in the outer layer, and contrasted MCNs with microcystic or serous cystadenomas,[2] describing the former as lesions with overt or latent malignancy and the latter as benign tumors. This was an important observation because, prior to that, pancreatic neoplastic cysts were simply referred to as cystadenomas and cystadenocarcinomas.

However, the presence of ovarian stroma was not considered a specific diagnostic criterion for MCNs, and as a consequence, for many years, MCNs and intraductal papillary mucinous neoplasms (IPMNs) were frequently confused.[3–6] Although the World Health Organization (WHO) defined and distinguished between IPMNs and MCNs as early as 1996 and emphasized the presence of ovarian stroma in MCNs,[7] it was not until recently, at a consensus conference held in Sendai, Japan, that the International Association of Pancreatology put forward guidelines requiring the presence of ovarian stroma to establish the diagnosis of MCNs.[8]

Using this criterion, we recently put together the surgical experiences of the Massachusetts General Hospital and the University of Verona.[9] Surgical specimens of all mucin-producing cystic lesions of the pancreas were carefully reviewed, and 163 patients who were identified with only lesions that had both an ovarian-like stromal layer and no communication with the pancreatic ductal system were included. These were mostly women (95%) and the MCNs were almost exclusively located in the body or tail of the pancreas (97%). None of the tumors were multifocal. The median age at the time of diagnosis was 45 years, with a range of 16 to 82. Twenty-five percent of tumors were incidentally discovered, 9% presented with acute pancreatitis (presumably from compression of the pancreatic duct) and

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the remaining with vague symptoms including mild abdominal pain. One hundred and eighteen of the tumors (72%) were classified as adenomas, 17 (10.5%) as borderline neoplasms, 9 (5.5%) as having carcinoma in-situ, and 19 (12%) as invasive carcinomas. This age and gender distribution, as well as the tumor location, is strikingly similar to those described in other published large series of MCNs where ovarian stroma has been a requirement for diagnosis[10–12]; the frequency of invasive cancer within these series has ranged from 7 to 36%.

By contrast, series of MCNs where ovarian-like stroma is not a requirement for diagnosis involve older patients, a higher proportion of males, and an even distribution throughout the pancreas,[3–6] which likely indicates inclusion of patients with branch duct IPMNs that appear to have a different biological behavior.[13]

In our study we found that malignant MCNs (both in-situ and invasive carcinoma) were significantly larger than benign ones (80 vs. 45 mm) and were 16 times more likely to harbor nodules (64 vs. 4%).[9] All MCNs with cancer were either greater than 40 mm in size or had nodules.

Management of Mucinous Cystic Neoplasms

A MCN should be suspected whenever a single cyst is seen by CT or MRI in the body or tail of the pancreas of a young or middle-aged woman. The wall of the cyst may appear thick, and an MRCP should show no communication with the pancreatic ductal system. If the demographics of the patient do not fit this pattern, or if the radiologic imaging is equivocal, then an endoscopic ultrasound (EUS) with aspiration of the cyst contents and biopsy of the wall is warranted. For an MCN, the EUS may show septations or nodules within the cyst, and the aspirate is characteristically thick and mucoid, with an elevated CEA level and a normal amylase. Cytology of the centrifuged cyst fluid or of the cyst wall may demonstrate mucinous epithelial cells. The main differential diagnosis is with unilocular serous cystadenomas (which have a low CEA in the fluid), solid pseudopapillary neoplasms (which often show necrotic debris within the cyst cavity), and branch duct IPMNs, which communicate with the ductal pancreatic system and therefore generally have an elevated cyst fluid amylase.

Surgical excison is indicated for all MCNs because extensive histological sampling (and, thus, certainty of benignancy) cannot be achieved until the tumor is excised. Whereas the risk of malignancy in tumors less than 4 cm and without nodules is low, the current thinking is that the majority, if not all of these tumors, will evolve into cancer if left untreated. This concept is based on epidemiological data showing that patients with invasive cancer within a MCN are older and have larger tumors.[3,6,10] This was also the case in our series, where patients with invasive mucinous cystadenocarcinoma had an average age of 55 years, compared to 44 years in the patients with noninvasive MCNs (adenoma, borderline tumors, and carcinoma in-situ).[9] Further evidence to this progression is derived from studies on the molecular pathology of these lesions indicating a stepwise increase in the frequency of K-ras and p53 mutations in a manner similar to that seen in the adenoma–carcinoma sequence of colon cancer.[14] If an expectant approach were to be followed, frequent surveillance with either CT or MRI would be required. Given the mean age of presentation of 45 years, this would not be cost-effective or practical.

Because most MCNs will be located in the body and tail of the pancreas, the appropriate operation is a distal pancreatectomy. A laparoscopic approach is a very good alternative for small or even medium-sized MCNs located in the tail of the pancreas,[15] but it is very important not to rupture the cyst during the procedure because spillage of contents could potentially lead to tumor spread. In addition, the cyst should be removed intact (i.e., not morselized) so the pathologist can do an appropriate examination. It may be reasonable to preserve the spleen in small or medium-sized lesions. There is no evidence to indicate that excision of lymph nodes beyond those immediately adjacent to the pancreas is necessary or beneficial even if there is a high suspicion of malignancy. In our series, none of the 19 cases with invasive carcinoma in our series had positive lymph nodes,[9] and a review of the literature failed to identify a single case with lymph node metastases. A similar biology is seen in ovarian MCNs, were the frequency of nodal metastases is less than 10%.[16,17] For MCNs that are located in the proximal body of the pancreas, close to the neck, a middle pancreatectomy is an option,[18] whereas some are amenable to enucleation.

Results of surgical treatment are excellent. Four recent large series, including ours, show that as long as there is no invasive carcinoma present within the specimen, the cure rate is 100%.[3,6,9,10] Because MCNs are never multifocal, there is no need for long-term surveillance after complete resection of noninvasive tumors. For patients with invasive mucinous cystadenocarcinoma, the 5-year survival in our series was 57%[9]; in other series, it has ranged from 30 to 63%.[3–6,10–12] There are no data on adjuvant treatment for these lesions.

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