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Current highlights on solid pseudopapillary neoplasm of the pancreas

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Abstract

Solid pseudopapillary neoplasm of the pancreas is a low-grade malignant tumor that predominantly affects young women in their third and fourth decade. Etiology and risk factors are unknown. Clinical symptoms are aspecific and most commonly due to mass effect. Diagnosis is made by computed tomography scan or magnetic resonance imaging and histological characterization is obtained by endoscopic ultrasound-guided fine needle biopsy. Microscopically, these lesions are composed by both solid and pseudopapillary structures with necrotic and hemorrhagic areas. Occasionally, the biological behavior is aggressive with tumor recurrence and distant metastasis. Usually, curative R0 surgical resection is the best option able to provide long term survival even in advanced disease. Unresectable disease is the main predictor of poor prognosis. Chemotherapy and radiotherapy regimens are not well standardized. However, they could be effective in reducing tumor size as neoadjuvant treatment or disease control in palliative setting. Although complete surgical resection provides a cure rate of > 95%, considering young age of the patients and morbidity associated to pancreatic surgery, further studies are needed to better investigate risk factors and responsiveness to hormones in order to allow early diagnosis and follow up strategies that could avoid unnecessary surgery in less aggressive disease.

Key Words: Pseudopapillary neoplasm; Pancreatic tumor; Pancreaticoduodenectomy; Distal pancreatectomy; Pancreas; Surgery

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Core Tip: This letter aims to underline the utmost importance of early diagnosis and standardization of treatment for a subset of rare pancreatic malignant tumors that affect young women and have good prognosis when curative surgery is performed. However, little is known about clinical behavior and hormonal responsiveness of such diseases and treatment option availability is still scarce for advanced, recurrent and metastatic disease so further investigation is claimed.

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TO THE EDITOR

We read with great interest the review written by Omiyale[1] which outlines the clinical and pathological features of solid pseudopapillary neoplasm of the pancreas (SPN) including the epidemiology, molecular pathology, cytology, differential diagnosis, treatment and prognosis.

As already reported by the aforementioned author, this is a rare tumor of uncertain histogenesis, known with several names or as Frantz tumor (after the name of who first described it) which accounts for 0.3% to 2.7% of all pancreatic neoplasms[2]. The author underlines the predominant incidence rate in young women.

Available data on this tumor behavior and prognosis are scarce and reported experiences are based on small number of patients or single case reports[3-7] even in high volume referral centers for pancreatic diseases. Nevertheless, no certain risk factors nor relationships with functional endocrine syndromes have been identified. SPN shows a bimodal incidence in women with two peaks at 28 years and 64 years and a unimodal behavior in men at 64 years[8]. Furthermore, recent studies described larger masses and more aggressive disease in men and post-menopausal women, suggesting an estrogen dependent behavior of these tumors[9,10]. These findings deserve further investigation in order to find out other possible non-surgical treatment options. It is very interesting to highlight that SPN are low-grade malignant tumors with an excellent overall prognosis and a curative rate of > 95% following complete surgical resection. It is worth emphasizing that although 10% to 15% of SPN have an aggressive behavior, the disease-free survival and overall survival are much better compared to other pancreatic tumors as long as R0 resection is achieved. Hao *et al*[11] in their review and metanalysis on a sample of 59 patients with aggressive SPN (one of the most consistent experiences available in literature) described a 5-year disease-free survival rate of 26.8% and a 5- and 10-year overall survival rates of 71.1% and 65.5%, respectively, with a recurrence or metastatic rate of up to 69.5%. This leads to the conclusion that about one third of patients affected by aggressive SPN will die of this disease. These consistent rates emphasize the outstanding importance of standardization of diagnostic tools and treatment procedures in order to guarantee early diagnosis and best therapy options to this small but challenging subset of patients[11]. Since the disease is often asymptomatic and symptoms are aspecific (mainly abdominal pain and distension) due to mass compression, the identification of homogeneous parameters able to predict an aggressive behavior is one of the major concerns in all the published studies. In fact, as reported by the author, diagnosis is mainly accidental and relies upon computed tomography (CT) scan and endoscopic ultrasound with fine needle biopsy for histological characterization. Often, SPN appears as a large (mean size 7.2 cm)[4] and heterogeneous mass (composed by both solid and cystic portions with fibrous septa, necrotic and hemorrhagic areas). A differential diagnosis of other exocrine or neuroendocrine pancreatic tumors can be challenging but crucial given the differences in clinical and prognostic behavior as well as treatment options. The tail of the pancreas seems to be the most frequent site of presentation although bifocal lesions have been sometimes reported. Based on these findings, Flores *et al*[8] proposed to classify SPN as follows: Unifocal SPN, referred to single lesions, bifocal SPN when there are two lesions and multifocal SPN when they are three[8].

Some authors emphasized the role of positron emission tomography-CT scan to better predict the aggressive pattern: An elevated standard uptake value seems to be correlated to higher Ki-67 expression ($> 3\%$)[12,13] that is sometimes reported to be a sign of aggressiveness[14,15]. However, while the role of aberrant Beta catenin expression is well known, the real prognostic meaning of Ki-67 expression is still not confirmed by the literature[16].

Histogenesis remains unclear and, although no specific immunochemistry pattern has been identified, most lesions show loss of positivity for E-cadherin and positivity for β -catenin, vimentin, alpha-1-antitrypsin, alpha-1-antitrypsin, CD10, CD117 and progesterone receptors. These characteristics may be added to the clinical, imaging and histological findings to provide diagnosis[8].

Curative resection, as conservative as possible, with both open or laparoscopic approach, is the best treatment option[17-19] providing long term overall and disease-free survival even in node positive patients[20]. Surgical planning is crucial and the classification proposed by Flores *et al*[8] could be useful in this matter[8].

Although overall and disease-free survival is good even in locally advanced and metastatic patients after curative (*i.e.* R0) resection, unresectable disease remain the most important predictor of poor survival in all experiences[11]. Given the low-grade malignancy of these tumors and the prognostic efficacy of surgery, non-surgical therapies have been scarcely investigated and no standardized protocol exists for this subset of patients. Some studies suggested the use of various drugs, in monotherapy or combinations, such as cisplatin, 5-fluorouracil, gemcitabine with uncertain results in recurrent, unresectable or metastatic disease[21,22]. Radiotherapy has been reported to reduce lesion size in little case series[21,23,24]. Despite this evidence, no standardized chemotherapy or radiotherapy regimen has been identified for unresectable, metastatic or recurrent patients. From this point of view, investigation into the possible estrogen-depending behavior of SPNs could perhaps open the way to new non-surgical treatment strategies.

Finally, the author reported a cure rate of $> 95\%$ following curative resection for these tumors even for advanced, recurrent and metastatic disease. However, since some other experiences described worsen overall and have a low disease-free survival and high recurrence rates[10], considering the young age of the patients and the relevant morbidity associated to pancreatic surgery, we strongly think that further studies are needed to better understand etiology, risk factors and hormonal relationships of this disease. This could improve early diagnosis, standardization of medical regimens thus limiting treatment invasiveness and it will help to identify patients with less aggressive disease who could benefit just from a strict follow up.

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