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Solid pseudopapillary tumor of the pancreas: Emphasis on differential diagnosis from aggressive tumors of the pancreas

Pankreasın solid psödopapiller tümörü: Pankreatik agresiv tümörlerden ayırıcı tanısının vurgulanması

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Solid pseudopapillary tumor is an unusual primary tumor of the pancreas with a low potential for malignancy and unknown cell origin, seen mostly in young women. Although it is discussed among pancreatic epithelial tumors, many cases do not express cytokeratin but show neuroendocrine differentiation. Three cases (2 female, 1 male, aged 24, 45 and 50 years, respectively) of solid pseudopapillary tumor localized in the pancreas are presented. All cases displayed a well-circumscribed tumor, with an average diameter of 6 cm and a red-brown colored, hemorrhagic, cystic cut surface. Microscopically they were encapsulated with large areas composed of thin papillary formations and solid areas focally. Tumor cells were dyscohesive with small, round-to-oval, central nuclei, and vacuolated, clear or eosinophilic cytoplasm without mitotic activity. NSE, vimentin, synaptophysin, ER, PR, Ki-67, S-100, Pan CK, a1-antitrypsin, a2-antichymotrypsin, and antibodies were used in the immunohistochemical study. Vimentin, synaptophysin, NSE, PR, and a1-antitrypsin showed expression in all cases, while Pan-CK was expressed in two cases. Ki-67 expression was below 1% in all cases. Morphologic features of solid pseudopapillary tumor may be confused with pancreatic endocrine neoplasm and ductal adenocarcinoma. All cases showed features of histocytic and neuroendocrine differentiation. Epithelial differentiation was identified in two cases. We conclude that immunohistochemistry is incapable of giving additional information for the diagnosis of solid pseudopapillary tumor due to different lines of differentiation of tumor cells. We believe that macroscopic and microscopic features (using hematoxylin and eosin stain) are more important for the diagnosis and differential diagnosis of this tumor.

Key words: Solid pseudopapillary tumor, pancreatic tumors, Frantz's tumor

Solid pseudopapiller tümör pankreasın nadir görülen primer tümörlerindendir. Genellikle genç kadınlarda izlenen, hücre orijini tartışmalı, düşük malignite potansiyeli olan bir tümördür. Pankreatik epitelyal tümörler arasında bildirilmesine rağmen çoğu olgu, sitokeratin ekspresyonu içermez, ve nöroendokrin diferansiyasyon gösterir. Bu çalışmada pankreasta lokalize, üç solid psuedopapiller tümör olgusu (iki kadın, bir erkek, sırasıyla 24, 45 ve 50 yaşlarında) sunulmaktadır. Olguların tümü makroskobik incelemede çevre pankreas dokusundan iyi sınırlanma gösteren, ortalama olarak 3 cm çaplı, kırmızı-kahverenkli, kanamalı, kistik özelliktedir. Mikroskobik incelemede kalın kapsüllü, geniş alanlarda ince papiller yapılar, seyrek solid adalar oluşturan, yer yer kohezyon kaybı gösteren küçük, yuvarlak-oval, santral nükleuslu, vakuollü, berrak, eozinofilik sitoplazmalı, belirgin mitotik aktivite göstermeyen hücrelerden oluşan tümöral gelişim izlendi. İmmünhistokimya ile NSE, vimentin, sinaptofizin, ER, PR, Ki-67, S-100, PanCK, CEA, CA 19-9, alfa-1 antitripsin, alfa-1 antikimotripsin araştırıldı. Vimentin, sinaptofizin, NSE, PR, alfa-1 antitripsin tüm olgularda, Pan CK ise iki olguda pozitif olarak izlendi. Ki 67 indeksi tüm olgularda %1'in altında bulundu. Solid pseudopapiller tümör morfolojik özellikleriyle pankreatik endokrin neoplazi ve duktal adenokarsinomla karışabilmektedir. Olgularımızın tümünde histiyositik ve nöroendokrin differansiyasyonu destekleyen ekspresyonlar gözlenmiş, epitelyal köken iki olguda saptanmıştır. Tümörün farklı differansiyasyon gösteren hücrelerden oluşması nedeniyle immünhistokimyanın ayırıcı tanıda yardımcı olmadığı ve solid pseudopapiller tümörün makroskopik özellikleri ile tanı ve ayırıcı tanısının yapılmasının gerekli olduğunu düşünmekteyiz.

Anahtar kelimeler: Solid pseudopapiller tümör, pankreatik tümörler, Frantz's tümörü

INTRODUCTION

Solid pseudopapillary tumor (SPPT) is a rare, benign tumor of the pancreas with unknown cell origin. These tumors are mostly seen in young women. Gruber-Frantz tumor, solid and cystic tumor, solid and papillary neoplasm are other terms given to SPPT. In 1996, the World Health

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Organization (WHO) renamed this tumor as SPPT for the international histological classification of tumors of the exocrine pancreas. We discuss diagnostic and differential diagnostic features of this unusual tumor and present three cases seen in our department.

CASE REPORT

These cases were diagnosed as SPPT in our department between 1999-2004. One case was a man aged 50 years, and two were women aged 24 and 45 years.

Clinical Features

All patients had nonspecific and similar clinical symptoms. The abdominal ultrasonographic findings of all three cases revealed a mass in the distal pancreas which was confirmed by abdominal computed tomography (CT) as a well-capsulated mass containing cystic components with heterogeneity in the distal pancreatic region. The greatest dimensions of these masses were recorded as 11, 4 and 3.5 cm radiologically. The masses were found to be sharply demarcated, well-circumscribed, and without any sign of invasion intraoperatively. Distal pancreatectomy with splenectomy was performed in two of the cases because of adherence to the spleen. Only a distal pancreatectomy was performed in the third case. All patients are alive with no recurrence or distant metastasis. The clinical data is summarized in Table 1.

Macroscopic Features

All three cases were characterized with a tumor that separated from the normal pancreas with a fibrous capsule. The cut surface was red-brown in color with focal areas of gray-white solid zones and small papillary formations. Some areas were hemorrhagic and cystic (Figure 1).

Microscopic Features

In all cases, the tumor separated from the normal pancreas with a fibrous capsule, but some areas were devoid of a capsule or it was rather thin (Figure 2A-B). Large areas of hemorrhage and cystic change obscured the presence of a capsule in some areas (Figure 2C). The tumor was composed of pseudopapillary structures in large areas with solid areas focally. Tumor cells were dyscohesive with uniform, small, round to oval, grooved, centrally localized nuclei and vacuolated or eosinophilic large cytoplasm. No mitotic activity was found. Some areas were characterized with cholesterol clefts, aggregation of foamy histiocytes, zones of hyaline degeneration and focal cytoplasmic hyaline globules (Figure 2D).

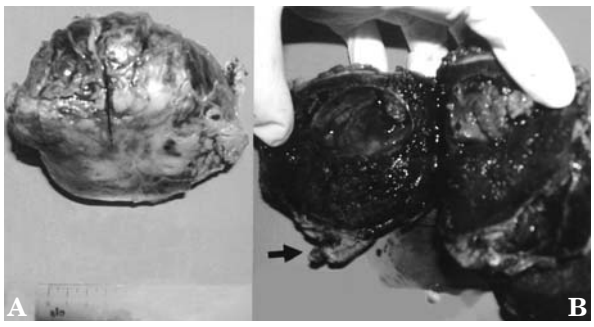

Figure 1. Macroscopic examination: **A)** Well-circumscribed tumor with pancreatic tissue at one side, **B)** Cut surface of tumor with a demarcation from the pancreas (arrow) with a thin fibrous capsule

All three cases were examined using immunohistochemical antibodies as given in Table 2. a1-antitrypsin (AAT), α1-antichymotrypsin (ACT), neuron specific enolase (NSE), synaptophysin (Synp)

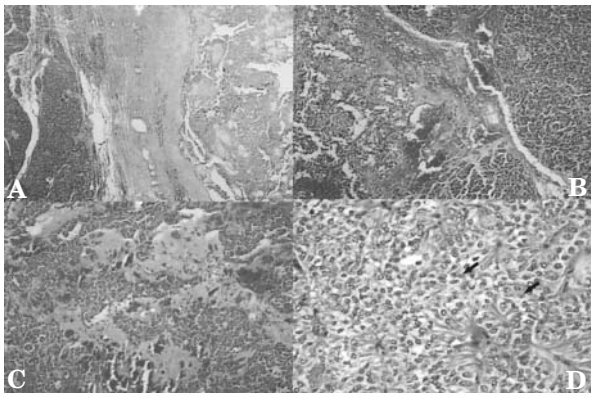

Figure 2. A) Broad fibrous capsule separating tumor from pancreas (H-E x 100), **B)** Areas devoid of a capsule (H-E x 200), **C)** Areas of hemorrhage and pseudocystic change (H-E x 200), **D)** Cytoplasmic hyaline globules (arrow) and cellular features (H-E x 400)

Table 1. Clinical data of three cases diagnosed as SPPT

Case	Age	Sex	Symptoms	Location	Size	Operation
1	50	Male	Abdominal pain	Distal pancreas	4x3.5x1 cm	Distal pancreatectomy + splenectomy
2	24	Female	Abdominal discomfort	Distal pancreas	3.5x1.5x1 cm	Distal pancreatectomy
3	45	Female	Abdominal pain	Distal pancreas	11x7x4 cm	Distal pancreatectomy + splenectomy

Table 2. Results of immunohistochemical staining procedures

	PANCK	Vimentin	AAT	ACT	NSE	S-100	Synp	CEA	CA19-9	Ki-67	ER	PR
CASE 1	+	-	+	+	+	-	+	-	-	1%	-	+
CASE 2	+	+	+	+	+	-	+	-	-	1%	-	+
CASE 3	-	+	+	+	+	-	+	-	-	1%	-	+

AAT: α1-antitrypsin, ACT: α1-antichymotrypsin, NSE: Neuron specific enolase, Synp: Synaptophysin, CEA: Carcinoembryonic antigen, PR: progesterone receptor

and progesterone receptor (PR) stained positive in all cases. No reactivity was observed with carcinoembryonic antigen (CEA) and CA-19-9. Pan CK and vimentin stained in two cases. Ki-67 proliferation index was below 1% in all cases. All cases were diagnosed as SPPT according to our results.

DISCUSSION

SPPT was first defined by Gruber Frantz in 1959. Since then, approximately 450 cases have been reported in the literature (1, 2). SPPT accounts for 1-2% of exocrine pancreas tumors (3), is usually asymptomatic with non-characteristic abdominal pain and may be seen in any localization of the pancreas (4).

SPPT is a well-circumscribed tumor with a diameter range of 1.5-30 cm (average 10 cm). The tumor is soft, yellow-red in color and consists of solid and cystic areas. Hemorrhage, cystic degeneration and irregularity in cyst walls can be seen. Microscopically both solid and cystic areas are seen. Cells have uniform, polygonal and epithelioid appearance, and round to oval, grooved, centrally localized nuclei with fine chromatin structure. Mitotic activity is not observed. Stroma is vascularized, areas of degeneration characterized with histiocytic infiltration, hemorrhage and cholesterol clefts are recognized, with cytoplasmic hyaline globules seen focally. Pseudopapillary structures are formed by the disintegration of tumor cells into pseudocystic cavities.

The cellular origin of SPPT is unknown. Many investigators believe it to arise from a multipotential primordial stem cell. The immunohistochemical profile of SPPT is not related to any of the pancreatic cells. This profile shows variation among different studies. In the current study all cases stained with AAT, ACT, NSE, Synp and PR. According to studies on SPPT, vimentin, NSE, and AAT are usually expressed. In this study, two cases showed vimentin expression. Vimentin expression is seen in more than 90% of these tumors, which shows that SPPT may have mesenchymal origin rather than a relationship with epithelial tumors of the pancreas. AAT expression may give rise to a suggestion of histiocytic origin, but according to one study, since no expression was determined with other histiocytic markers, a histiocytic origin cannot be claimed (9). AAT expression is also seen in other pancreatic tumors such as acinar cell carcinomas and endocrine tumors, but unlike in SPPT the staining is weak and non-specific. Cytokeratin expression shows variation in different studies, usually below 30%, rarely around 60% (6, 9). The low rate of cytokeratin expression, great variation among different studies, and high rate of vimentin staining in SPPT makes it difficult to relate it to any of the epithelial components of the pancreas. The usual reactivity of NSE, focal identification of Synp expression, no reaction with chromogranin A, and absence of hormone synthesis or any clinical endocrine dysfunction denotes that SPPT is not a neuroendocrine tumor but instead shows only focal neuroendocrine differentiation (9). We observed reactivity in our cases with NSE and Synp, while no expression was found with S-100. Reactivity with markers specific for pancreatic ductal epithelia such as CA19-9 and CEA are usually not observed in SPPT. Our cases did not show any reactivity with these markers (10). These results confirm that SPPT cannot be related to pancreatic ductal epithelia. The strong preponderance in young women and usual expression of PR suggests that during early embryogenesis, especially the left genital ridge cells come in contact with the pancreas and gain a different line of differentiation. This idea leads to the hypothesis that SPPT might have originated from these cell lines (3, 6, 8). PR showed nuclear staining focally in all cases.

In the current study, a diagnostic immunohistochemical profile for SPPT could not be demonstrated. Consistent with our results, case presentations in the literature have achieved different immunohistochemical expressions; therefore, a diagnostic profile cannot be reported. We observed that histomorphologic features of this tumor are rather characteristic, and differential diagnosis via immunohistochemistry is not helpful.

Although capsular, vascular and nerve sheath invasion, nuclear pleomorphism, and prominence of mitotic activity may suggest aggressive behavior, the prolonged natural history and relative rarity of the tumors make it difficult to establish histopathologic criteria predictive of aggressive potential. Only distant metastasis can be accepted as a criterion of malignancy. We believe that commenting on the presence or absence of capsular invasion is rather difficult and a subjective criterion. In our cases, some areas were devoid of a capsule due to hemorrhage, cystic degeneration, dyscohesive cellular islands and existence of recurring areas of fibrosis and hemorrhage. Differentiating capsular invasion from degenerative changes in areas probably having a true fibrotic capsule was an impossible task. We thus believe that defining capsular invasion as a criterion of malignancy does not seem meaningful. Local invasion, distant metastasis and recurrence are very rare. The reported rate of metastasis is 15% and for recurrence is 2-6%. Long-term survival rates are reported for cases with metastasis. An intensive follow-up is recommended for such cases (1, 3, 6-8). Only two cases of mortality due to SPPT have been reported. Both cases were microscopically composed of large areas with sheet-like pattern, nuclear pleomorphism and prominent mitotic activity. One case had a focus of sarcomatoid carcinoma and the other had lymph node metastasis.

Differential diagnosis of SPPT includes ductal adenocarcinoma, neuroendocrine tumors and pseudocysts of the pancreas. If SPPT is not considered, and if there is a lack of awareness of its histopathologic features, insufficient sampling of the tumor and absence of clinical findings, then confusion with ductal adenocarcinomas is rather probable. Since SPPT is known for its good prognosis, and surgical excision is curative, differential diagnosis from ductal adenocarcinoma and neuroendocrine tumor is essential (2, 6, 8). The characteristic macroscopic and microscopic features of SPPT make differential diagnosis easy. Ductal adenocarcinomas are mostly seen in elderly men. They are much smaller than SPPTs. Microscopically, ductal and glandular structures form the tumor. They grow in a infiltrative manner with capsular circumscription. Neuroendocrine tumors usually present with a solid or microacinar pattern. Hemorrhage and pseudocystic areas are not usually observed. Nuclei are small, round, smoothly contoured and possess fine chromatin structure. SPPT may be confused macroscopically with pseudocyst unless sufficient sampling is undertaken. Characteristic microscopic features of SPPT allow easy differential diagnosis.

In conclusion, differential diagnosis of SPPT, a tumor which may reach large dimensions with a benign behavior and which is curable by surgical excision, from other tumors with aggressive behavior seen in the same localization is important. Our results show that diagnosis depends on awareness of clinical, macroscopic and microscopic features and sufficient sampling of the tumor. Histopathologic diagnosis can be made with a routine hematoxylin-eosin staining. The variation in immunohistochemical findings and absence of a specific profile denote that immunohistochemistry is incapable of giving additional information for the diagnosis of SPPT.

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