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Research Paper

The clinicopathological and immuohistochemical analysis of solid-pseudopapillary tumor of the pancreas: report of 9 cases

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Abstract

Objective: To investigate the clinical features, pathological characteristics and immunophenotype of solid-pseudopapillary tumor of the pancreas(SPTP). **Methods:**Nine surgically treated cases of SPTP were retrospectively reviewed. Hematoxylin and Eosin(HE) staining and immunohistochemical staining were used to analyze all cases, and the general clinical data was collected. **Results:**Six patients were asymptomatic except for a palpable mass. Two patients complained of vague-epigastric pain. One patient appeared jaundice. The tumor was encapsulated and solid tissues alternately with cystic tissues. Histologically, the histological structure of solid portion was pseudopapillary with a fibrovascular core. Tumor cells were uniform and medium-sized which were arranged in sheets ets or nests or pseudopapillary patterns. Immunohistochemical studies demonstrated that SPTP proved positive in vimentin(9/9 cases), AAT(9/9 cases), NSE(9/9 cases), ACT(7/9 cases), CK20(2/9 cases), CgA(1/9 cases), S-100(3/9cases), PR(4/9cases), Syn(3/9 cases) and CD56(5/9cases), negative in CEA and ER. **Conclusion:**SPTP is a tumor predominantly occurring in young women frequently without special symptoms. This tumor has various characteristical histological patterns with different immunophenotype.

Key words: pancreatic neoplasm; solid-pseudopapillary tumor; pancreas

INTRODUCTION

Solid-pseudopapillary tumor of the pancreas(SPTP) is one of the less frequently found primary tumors of the pancreas which is still an enigmatic neoplasm[1,2], and the term encompasses the two histological features: solid and pseudopapillary areas. The tumor has been given several different names according to its macroscopic and microscopic pathological character until this name, solid-pseudopapillary tumor of the pancreas, was defined by the World Health Organization(WHO) as unique tumor in 1996[3-5]. Although the pathogenesis of SPTP is still controversial, the disease is generally considered to have a benign clinical course with low malignant potential[6]. Its origin is still controversial although a ductal origin has been favored[7]. We tried to describe its clinical features, pathological characteristics and immunophenotype as clearly as possible and enhance the clinicopathological awareness of SPTP.

MATERIALS AND METHODS

Study population

We retrospectively reviewed a series of 9 SPTP cases managed in Affiliated First Hospital of Fujian Medical University from 1997 to 2007. All patients underwent tests of blood sugar, serum and tumor markers(AFP, CEA, CA19-9, CA242, and CA50) regularly. Among these 9 patients, 8 were female and 1 was male. The tumors were resected by local tumor resection(4/9), distal pancreatectomy(1/9), distal pancreatectomy with splenectomy(3/9) and pancreaticoduodenectomy(1/9). All tumor specimens were confirmed pathologically by

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at least two senior pathologists independently.

Histopathology and immunohistochemistry

Pathological features of SPTP were observed through the tissue sections stained by Hematoxylin and Eosin staining method. Immunohistochemical staining(SP method) was used to analyze the immunophenotype of SPTP. The tissue sections were stained with a panel of antibodies used in the routine work-up of SPTP. All reagents were bought from Fuzhou Maixin Biological Technology Limited Company. Appropriate positive controls(cases known to be positive for all antibodies used in the study) were run in parallel.

RESULTS

Clinical experience

The tumors were 8.9 cm in diameter on average (arrange 4 to 11.6 cm) and located in the body(4 cases), or the tail(2 cases) or head(3 cases) of the pancreas. Mean age of the patients was 21.7 years(age range 18 to 32 years). Only one patient was male, and the others were female. Six patients were asymptomatic except the palpable tumor detected by physical examination. Two patients complained of vague-epigastric pain. One patient complained of abdominal pain(displaying jaundice accompanied with the damage of liver function). The tumor markers were all within normal limit.

Pathological features

Grossly, the tumors were globular or oval, surrounded by a fibrous capsule. The cut surface of the tumors was found to be heterogeneous with solid and cystic components. The cystic components were chiefly filled with reddish-brown hemorrhagic debris in six cases. The typical histopathological appearance of SPTP was distinctive among other primary pancreatic neoplasms. They were composed of papillary and microcystic solid structures, with neoplastic epithelial cells polygonal in form, consistent in size, and un-cohesive in nature. No mitoses or atypical cells were found. Some mass were characterized by solid areas, which alternated with the pseudopapillary structure(***Fig 1***) with a fibrovascular core surrounded by several layers of epithelial cells and cystic spaces caused by degenerative changes in the solid neoplasm. Tow smaller tumors in our group were often arranged in solid sheets with a rich microvasculature. In the center of pseudo-papillary area, there was mucus degeneration. Other special forms were seen, including eosinophilic globules, myxoid change in the stroma and cholesterol clefts with multinuclear giant cell reaction. Some of the cystic areas display hemorrhage(***Fig 2***), calcification and necrosis. There was infiltration of the tumor cells into the capsule and the surrounding nor-mal pancreatic parenchyma that were observed in 2 cases.

Immunohistochemistry

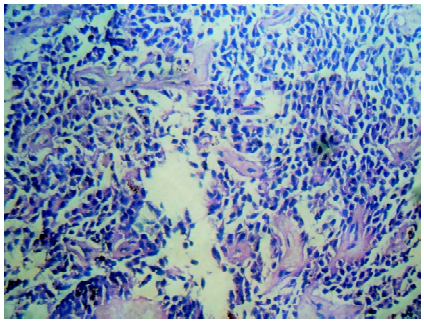
The slides were stained with the following commercially available antibodies: vimentin, alpha-1-antitrypsin (AAT), neuron-specific enolase(NSE), chromogranin (CgA), alpha-1-antichymotrypsin(ACT), synaptophysin (Syn),CD10,CD56,CK20,S-100,CEA,ER and PR. Immunoh-istochemically, all the tumors were vimentin (***Fig 3***) and AAT (***Fig 4***) diffusely positive(50% or more of the tumor cells staining). NSE showed focal positivity in all cases with 10-50% of tumor cells displaying immunolabeling. All cases were negative for CEA and ER. Similarly, SPTP proved positive in ACT(7/9 cases), CK20(2/9 cases), CgA(1/9 cases), S-100(3/9cases), PR (4/9cases), Syn(3/9 cases) and CD56 (5/9cases).

CONCLUSION

SPTP is a rare disease that is usually presented in young females with a reported incidence of 0.13% to 2.7% of all pancreatic tumors[8-9]. The incidence of this neoplasm may be increasing since more and more cases are being reported, with more than two thirds of the total cases described in the last 10 years. It was reported that approximately 9% of the patients were asymptomatic and that most of them had the sole clinical experience of the palpable abdominal mass[10-11]. The blood of all the patients in our group, including the tumor markers, tested normal with only one exception. This abnormal patient represented jaundice and the damage of liver function, because the tumor squeezes the common bile duct and gets it obstructed and dilated.

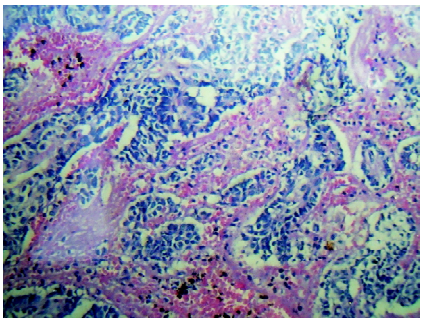
In this investigation, we found that light-microscopic features of SPTP were unique and generally no pathologic diagnosis problem presented, although on gross examination degenerative cystic changes might be confused with cystic neoplasms or a nonfunctioning islet cell tumor of the pancreas. The typical microscopic pathologic structure was a pseudopapillary structure with a fibrovascular core and mixed structure with a solid and cystic component. The cells of SPTP also had characteristic as mentioned above. In 2 cases, the capsule or the surrounding normal pancreatic parenchyma was infiltrated, which could be considered as malignant potential[12]. The biological behavior of SPTP is undetermined, borderline or malignant potential. Even the capsule and the surrounding normal pancreatic parenchyma were found invaded in some cases, prognosis was still good. SPTP is an indolent neoplasm with low-grade biological aggressiveness[13].

In our immunohistochemical studies, all the tumor cells reacted positively with vimentin, NSE and AAT. Staining of CK20, CgA, S-100, ACT, PR, Syn and CD56 were focal or faint. These positive staining antibodies included ductal marker (CK20), exocrine marker of



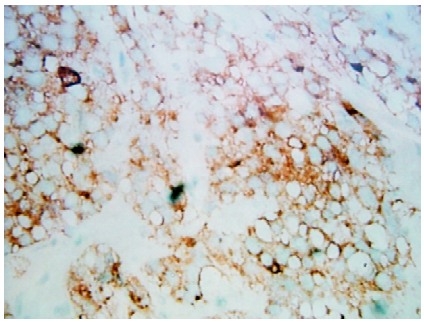
Histological view of SPTP shows uniform cells arranged in solid and pseudopapillary pattern.

Fig 1 Pathological features of SPTP(HE, × 200)



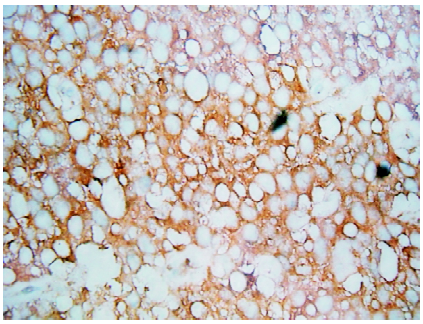
Histological view of SPTP shows pseudopapillary structure with abundant red blood cell among them.

Fig 2 Pathological features of SPTP(HE, × 100)



Immunohistochemical view of SPTP shows vimentin positive

Fig 3 Immunohistochemistry of SPTP(SP, × 400)



Immunohistochemical view of SPTP shows AAT positive.

Fig 4 Immunohistochemistry of SPTP(SP, × 400)

acinar differentiation(AAT, ACT), neuroendocrine marker (Syn, NSE, CD56) and mesenchymal marker (vimentin, S-100). Based on these results, we failed to find out a clear phenotypic relationship with any of the defined cell lines of the pancreas or discern a line of cellular differentiation for SPTP. It was still an enigma, but most of pathologists considered that SPTP came from pluripotent stem cells. The tumor postulated differentiation along endocrine cell lines on the basis of NSE positive, but the expression of vimentin did not support this interpretation[14]. The female predominance along with the presence of progesterone receptor in some reported cases did not suggest that female hormone should be blamed for the origin of the tumor[15]. We suspected that the tumor cells perhaps had the ability of multi-differentiation. Other investigators[14] postulated that SPTP may be derived from genital ridge/ovarian anlage-related cells which were attached to the developing pancreas in early embryogenesis instead of pancreatic cell origin.

In conclusion, SPTP might originate from ductal and acinar pancreatic cells, endocrine cells or pluripotential stem cells, but present findings showed that it is still an enigma. More studies should be performed to elucidate the essential characteristic.

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· Science Report ·

Constructing and packaging scAAV vectors and detecting their transduction efficiency

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Gene therapy is a form of molecular medicine that promises to provide new treatments for a large number of inherited and acquired diseases. One of the biggest stumbling blocks to successful widespread application of genetic treatments is the development of safe and effective vectors with which to ferry genetic material into cells. Adeno-associated virus (AAV), a nonpathogenic human parvovirus, has gained attention as a potentially safe vector for gene transfer and gene therapy. The AAV genome is a single-stranded DNA, which is transcriptionally inactive. It has been reported that viral second-strand DNA synthesis is the rate-limiting step in AAV-mediated transgene expression. Self-complementary adeno-associated viral(scAAV) vectors bypass the requirement for viral second-strand DNA synthesis, and lead to a significant increase in transduction efficiency. scAAV vectors have been successfully constructed by Xiao and Smulski in the USA in 2003. Recently, we have developed and packaged scAAV, and reported as following.

Several endonuclease were used to remove the D-sequence, terminal resolution site(Trs), Rep and Cap gene of pSub201 to develop plasmid of scAAV. The plasmid of scAAV constructed by us, which contain 2.4 kb exogenous gene including CMV promoter driving hrGFP gene (CMVp-hrGFP), named pJQ2. Plasmids of pJQ2 and pAAV-hrGFP were respectively transfected into adenovirus transformed 293 cells, using the calcium phosphate triple-plasmid transfection protocol. Low relative molecular mass(low-Mr) DNA samples were isolated 72 h post-transfection by the procedure described by Hirt, digested extensively with DpnI and analyzed on Southern blots with a ^{32}P-labeled hrGFP-specific DNA probe. It is evident that efficient rescue and replication of the recombinant AAV genome, represented by the characteristic monomeric(m) and dimeric(d) replicative DNA intermediates, occurred from both of pJQ2 and pAAV-hrGFP. Then, scAAV vectors were produced by the calcium phosphate triple-plasmid transfection protocol. The ratios of double-stranded (ds) and single-stranded(ss) AAV vectors were determined by electrophoresis on 1% alkaline agarose gels followed by Southern blot analysis with a ^{32}P-labeled hrGFP DNA probe. The results suggested that most of pJQ2 was successfully packaged into scAAV vectors, while pAAV-hrGFP was packaged only in single stranded AAV vectors. The titers of vJQ2 are similar to those of vAAV-hrGFP packaged at same time. In addition, the transduction efficiency in 293 and HeLa cells were measured in 48 h post-infection by fluorescence microscope. The transduction efficiency of vJQ2 vectors was increased to 5-fold and 14-fold in 293 and HeLa cells, compared with conventional AAV.

In summary, we have constructed and packaged double-stranded AAV, which has implications in the optimal use of recombinant AAV vectors in human gene therapy, and will promote the study in AAV mediated gene transfer.

Key words: gene therapy; self-complementary adeno-associated viral; transduction efficiency

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