Assessment of guidelines to improve diagnosis and treatment of solid pseudopapillary tumor of the pancreas

A case report and literature review

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Assessment of guidelines to improve diagnosis and treatment of solid pseudopapillary tumor of the pancreas. A case report and literature review

AIM: *Solid pseudopapillary tumor (SPT) of the pancreas is a rare neoplasm, its preoperative diagnosis is difficult and therefore inappropriate therapy or postoperative complications are frequent. Reviewing the literature, the purpose of this article was to identify guidelines to improve diagnosis and treatment of SPT.*
CASE REPORT: *Authors report a case of SPT of the pancreas in a 27 year-old woman in whom a mistaken radiologic diagnosis made surgical strategy difficult and caused postoperative complications.*
DISCUSSION/CONCLUSIONS: *Clinicians and surgeons should: 1) consider the possible disease of SPT in young females, with pancreatic encapsulated lesion with well-defined borders and variable central areas of cystic degeneration, necrosis or hemorrhage showed on radiological examinations. 2) Intensify the differentiation of the clinical symptoms, especially during the course of therapy of chronic gastritis and diabetes. 3) Use immunohistochemical stains of alpha-1-antitrypsin, alpha-1-antichymotrypsin, vimentin and neuron-specific enolase. 4) Keep this unusual but potentially curable tumor in mind, following patients who had suffered from acute pancreatitis or abdominal injury. Increasing experience with this tumor leads to a greater awareness of its clinical presentation and pathological features and a lower rate of misdiagnosis. 5) Finally, perform, where technically feasible, conservative surgical treatment, that is safe and effective.*

KEY WORDS: Diagnosis, Pancreas, Solid pseudopapillary tumor, Surgery.

Introduction

Recently there has been a steady increase in the number of solid pseudopapillary tumors (SPT) of the pancreas, with more than two thirds of the total cases described in the last 10 years [1]. With the present paper, 913 cases of SPT were described in 254 articles in the world literature, updated to October 2007. However, clinicians and surgeons are often lacking in knowledge of this rare disease, so preoperative diagnosis is difficult and inappropriate therapy or postoperative complications are frequent. Cheng et al. [2] reported a misdiagnosis' rate of 45.5% in their series. This rate was 66.7% in their patients under 30 years.

We report a case of SPT of the pancreas in a young woman in whom a mistaken radiologic diagnosis made surgical strategy difficult and caused postoperative complications. Because of the lessons learned from this patient, the aim of this article was to identify guidelines to improve diagnosis and treatment of this rare neoplasm. We pointed out the pathogenesis' theories and the reasons of misdiagnosis; we described the role of diagnostic imaging procedures and immunohistochemical stains in differential diagnosis. Besides, we focused on the criteria determining malignant behaviour of SPT and surgical treatment of this tumors.

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Case report

A 27 year-old woman was admitted to our hospital in August 2002, complaining of a long history of vague-visceral pain and bloating. Her medical history referred neither to previous episodes of acute pancreatitis, nor abdominal trauma. The patient did not report weight loss. Clinical examination found a large abdominal mass in the left upper quadrant. Blood tests were unremarkable. Serum tumor markers gave the following findings: carcinoembryonic antigen (CEA) 2.2 ng/ml (normal range [n.r.] < 6 ng/ml), cancer antigen (CA 19.9) 49.5 (n.r. < 37 U/ml), (CA 125) 44 (n.r. < 35 U/ml) and (CA 72.4) 3.7 (n.r. < 3 U/ml).
An abdominal ultrasound (US) examination detected a 9.5 x 8 cm. solid, round lesion with a homogeneous echo-pattern and moderate internal vascularization. The tumor was in close contact with the anterior margin of the left kidney and involved the pancreatic body-tail. No other masses were detected in the head of the pancreas or in the bile duct. The mass displaced splenic artery and vein. Angio-spiral volumetric computed tomography (CT) and magnetic resonance imaging (MRI) scans showed a large (9 cm.), round, well encapsulated parenchymatous mass with calcifications and necrotic areas. The lesion abutted the posterior wall of the gastric body, adhered to and displaced the pancreatic body-tail and the splenic vessels. A clear cleavage plane separated the mass from the spleen and from mesenteric and left renal vessels. No liver nor lymph nodal metastases were detected (Fig. 1). These findings suggested a malignant leiomyoma of the gastric body with complete extraluminal growth. An upper gastrointestinal endoscopy showed only apparently extraluminal compression of the posterior wall of the gastric body, without gastric erosions or other macroscopic lesions.

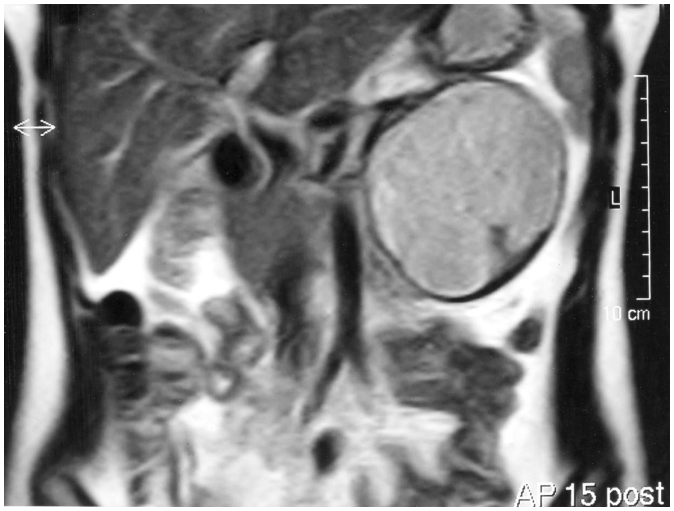

Fig. 1: Magnetic Resonance Imaging showed a large (9 cm. in diameter), round, well encapsulated parenchymatous mass with calcifications and necrotic areas. The lesion abutted the posterior wall of the gastric body, adhered to and displaced the pancreatic body-tail and the splenic vessels.

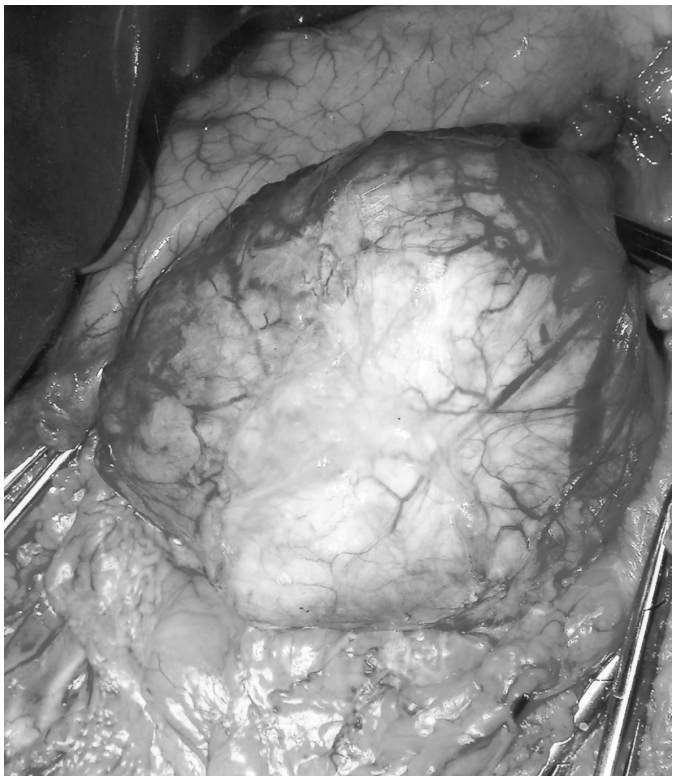

Fig. 2: Intraoperative picture. The lesion, a round mass of 10 cm. in diameter, was located behind the stomach, but did not adhere to it, and apparently arose from the lower edge of the pancreatic body.

The patient underwent bilateral subcostal laparotomy in August 2002. The lesion, a round mass of 10 cm. in diameter, was located behind the stomach, but did not adhere to it, and apparently arose from the lower edge of the pancreatic body (Fig. 2). These findings raised the possibility of a pancreatic or an extra-pancreatic tumor without a clear cleavage plane from the pancreas. Intraoperative pathologic examination of the frozen sections failed to define the histologic type of the tumor. Celiac axis lymph nodes contained only inflammatory tissue. An enucleation was performed and the lesion was removed with a pancreatic marginal resection 8 cm. long and 1 cm. deep. The pancreatic cut edge was closed by hand-sewn absorbable interrupted suture (polygalactin 3/0). Total parenteral nutrition (TPN), antibiotic therapy (ceftriaxone 2 g. i.v.) and gabesate mesilate infusion (600 mg./die) were started after surgery. The postoperative course was complicated by a pancreatic fistula. An abdominal US showed a perisplenic and left perirenal fluid collection consisting of a clear watery secretion. On the 5th POD a percutaneous 14 French drainage catheter was placed under US guidance. The presence of a pancreatic fistula was confirmed by the amylase level in the drainage fluid (> 100,000 U/L). Antibiotic therapy was switched with gentamicin (160 mg./day), clindamycin (1.2 g./day) and fluconazole (200 mg./day). Fever continued until POD 15. On the 31st POD, when the mean drainage output decreased to 125 ml./day, TPN was

changed with enteral nutrition (EN). On POD 45 the patient was discharged receiving EN, with the intra-abdominal catheter still in place. Three weeks later, fluid collection and drainage output ceased and the drainage catheter was removed. EN was gradually switched to a low fat oral diet.

Histopathologic studies of the surgical specimen showed a round tumor measuring 10 cm. in diameter, surrounded by a fibrous capsule. The cut surface was partly dark grey and diffusely hemorrhagic. Microscopic examination of the surgical specimen showed a proliferation of monomorphic, medium-size neoplastic cells, with a round nucleus and granular cytoplasm. The neoplastic cells showed partially solid and trabecular cellular growth with cystic areas and partial ulceration of the outer capsule. Immunohistochemical studies suggested the diagnosis of a nonsecretory neuroendocrine pancreatic tumor (positive staining for cytokeratin, vimentin, neuron-specific enolase (NSE), alpha-1 antitrypsin, chromogranin, synaptophysin and N-CAM, but negative for S-100, HBA-71, insulin, vasoactive intestinal peptide, pancreatic polypeptide, gastrin and somatostatin). A further histopathologic study showed intensive staining for alpha-fetoprotein and no staining for alpha 1-antichymotrypsin, without vascular invasion, perineural lymphangitis or deep tissue penetration. After reviewing and discussing the controversial immunohistochemical findings and the ultrastructural study of the intracellular features, the pathologists reached a consensus and diagnosed a solid pseudopapillary tumor of the pancreas. At 5-years and 6-months follow-up, the patient is disease-free and in good health.

Discussion

SPT of the pancreas is a rare exocrine pancreatic tumor, first described by Frantz in 1959 [3], with an incidence rate of 0.17-2.7% of primary pancreatic tumors. SPT affects most commonly young women (82%) with the peak incidence during the second and third decade of life (mean age 27 years), with only about 7-8.3% of all cases reported in males. The male: female ratio is 1: 9.5. It tends to be fairly benign in young females but appears to be more aggressive in older males.

The seeming tendency of SPT to affect young women has suggested to some that the pathogenic basis of SPT may be influenced by sex hormones. Indeed, the rate of growth of SPT is accelerated during pregnancy. However, there are no significant qualitative differences in immunohistochemical stains for sex hormone-receptor proteins or in clinicopathologic characteristics attributable to gender alone [4].

Many investigators favour the theory that SPT originate from multipotent primordial cells [5] while others suggest an extra-pancreatic origin from genital ridge angle-related cells [6]. The tumor cells may be derived from the celomic epithelium and rete ovarii. These stem cells may become attached to pancreatic tissue during early embryogenesis. So, despite the increase in recognition of SPT, reported during the last ten years, the pathogenesis remains uncertain.

An apparent rise in the incidence of these tumors is probably due to a better awareness of the pathology, that in 1996 the World Health Organization renamed SPT for the international histological classification [7], and to a larger availability of immunohistochemical stains.

But, although the diagnosis of solid pseudopapillary neoplasm should at least be suspected in young women with a solid and cystic or large solid pancreatic mass, definitive preoperative diagnosis can be difficult. The reasons of the misdiagnosis are as follows: 1) Because SPT has a low incidence of 0.17% to 2.7% among pancreatic tumors, clinicians and surgeons are usually lacking in knowledge so it is easy to ignore and it may not even considered in the preoperative, intraoperative or postoperative diagnosis. Several lesions may be misinterpreted histopathologically as atypical pancreatic neoplasms. Peng et al. [8] reported that SPTs diagnosed by intraoperative frozen section in their group were only 44%. So, diagnosis depends on awareness of macroscopic and microscopic features and sufficient sampling of the tumor, too [9]. Grossly, SPT is a well-encapsulated, spherical mass, usually measuring around 8 to 10 cm. The cut surface shows large spongy areas of hemorrhage alternating with both solid and cystic degeneration. Microscopically, the growth pattern of the tumor is remarkably uniform, with a combination of solid, pseudopapillary, or hemorrhagic pseudocystic structures in various proportions. 2) The exophytical tumour grows slowly as it expands and could even extend to the retroperitoneum and be misdiagnosed as a retroperitoneal malignancy. 3) This disease has no peculiar clinical characteristics. So, early diagnosis is difficult. 4) The influence of medical history may be noteworthy, especially in patients that suffered from traumatic haematoma or inflammatory pseudocystic tumour because of recurrent pancreatitis. 5) Inexperience is another reason for failing to detect SPT. 6) Finally, young people is inclined to be misdiagnosed.

Differential diagnosis of SPT includes pancreatic neuroendocrine tumor, acinar-cell carcinoma, pancreatoblastoma, serous microcystic adenoma, papillary mucinous carcinoma and calcified hemorrhagic pseudocyst [10].

Approximately 64% of these tumors arise in the body-tail of the pancreas with a mean diameter of 10.3 cm. [11]. Clinically, SPT may present as a palpable upper abdominal mass with discomfort or non-specific symptoms of vague visceral pain or swelling in the epigastrium, as in our case. Some patients are completely asymptomatic (48%) and SPT may be an incidental finding during diagnostic imaging procedures as high as 27.3%. Usually there is no evidence of pancreatic insufficiency, abnormal liver function tests, cholestasis, elevated pancreatic enzymes or an endocrine syndrome. Tumor markers are also unremarkable.

On radiological examinations both a capsule and intra-

tumoral hemorrhagic degeneration are important clues to the diagnosis because they rarely are found in other pancreatic neoplasms [12].

CT shows an encapsulated lesion with well-defined borders and variable central areas of cystic degeneration, necrosis or hemorrhage. Calcifications may occasionally be seen (in up to 30% of cases). After intravenous contrast administration, CT shows areas of solid enhancement peripherally, whereas cystic spaces are centrally located. However, Sun et al. [13] reported a CT scan accuracy of only 76.4%.

Because of its superior contrast resolution, MR is better than CT for distinguish certain tissue characteristics, such as hemorrhage, cystic degeneration, or the presence of a capsule. MR imaging features can be highly suggestive for the diagnosis of SPT. Infact, MR accuracy is 90.9%. This tumor should be considered when a well-marginated, large, encapsulated, solid and cystic mass with areas of hemorrhagic degeneration and progressive peripheral or slightly heterogeneous contrast enhancement, seen after gadolinium administration on dynamic examination, is detected in the pancreas of a young woman [14].

Immunohistochemical stains are used for study of SPT. Stains of alpha-1-antitrypsin, alpha-1-antichymotrypsin, vimentin and NSE are often positive. Lai et al. [15] reported 84% positivity for NSE, 83% for alpha-1-antitrypsin and 72% for vimentin. Immunohistochemical stains for CEA, CaA 19.9, alpha-fetoprotein (AFP) and P53 are usually negative. Our patient presented positive staining for cytokeratin, vimentin, NSE, alpha-1 antitrypsin, chromogranin, synaptophysin and N-CAM.

Because of the low grade malignant potential and good prognosis after complete resection of the tumor, it is important to make a correct diagnosis before operation [16].

Besides, following misdiagnosis, the course of disease is lengthened significantly (P= 0.029). The gradually enlarging SPT with a long growth time brings obvious difficulties to the operation. Inconclusive preoperative findings usually are of no help for the surgeon who can only decide on the extent of the intervention intraoperatively. In the misdiagnosed group, the medical expenses are greater and the days in hospital prolong significantly (P = 0.043) [2], as in our case.

The low grade of malignancy of this tumor and because the mass is usually surrounded by a dense fibrous capsule, led some surgeons to perform simple enucleation of the neoplasm. In Japan 35% of SPT's originating in the pancreatic head have been treated with enucleation and over 60% have been resected by a pylorus-preserving pancreato-duodenectomy [17]. The choice of the local tumor resection, pancreatic segment resection or radical resection depends on the judgment about tumor's invasive feature or the integrity of tumor's capsule (P = 0.0099), whereas the operative types in radical resection depend upon the tumor's position in the pancreas (P = 0.0011). However, particular emphasis should be placed on carefully anatomizing the pedicel or root of the tumor to excise it completely and avoid residual tumor or injury the normal pancreas. Surgery is usually curative for localized disease. Intra-operative frozen section may be helpful to ascertain the adequate of the resection margins, but diagnosis always depends on the pathologist experience. Even if the disease is extensive at the time of presentation, surgical debulking favors prolonged survival. Infact, invasion to the portal vein or superior mesenteric artery should not be included as a criterion for nonresectability of these neoplasms. Extensive lymphatic dissection or more radical local approaches are not indicated. For the metastases, surgical debulking should be performed. Compared with curative resection, enucleation of benign cystic pancreatic neoplasms reduces operative time and blood loss, but has a high incidence of postoperative pancreatic fistula (as in the case presented).

Most SPTs have an indolent clinical course and following successful surgical resection appear to have a greater than 97% 5-year-survival. Papavramidis et al. [17] reported that overall 2-year survival rate for SPT's (with metastases or not) was 97% and 5-year survival around 95%.

Nevertheless, it is reported that 6.5% of SPT present with local recurrence or major organ invasion and 5.5% have metastases. Indeed, even in the event of metastasis, the lesions are slow growing and are associated with long-term survival. The overall mortality rate of the disease is approximately 1.5% [18].

Many studies have attempted to delineate the pathologic criteria necessary to identify SPTs with metastatic and recurrent potential. Tang et al. [18] reported that identification of prognostic features is difficult because of rarity of these neoplasms. These have included deep extra-pancreatic invasion, vascular or perineural invasion and lymph node metastasis. Pathologic features that are likely associated with unusually aggressive clinical behaviour include: a diffuse growth pattern with extensive tumor necrosis, an unusually high mitotic rate and the presence of an undifferentiated component [19]. Peng et al. [8] showed that the incidence of malignancy among SPTs of the pancreas was about 12%, similar to the 14.7% reported by Mao et al. [20]. The most common site of metastasis is the liver (42%), peritoneum (42%) and lymph nodes (25%). Kang et al. reported [21] that 33% of patients with SPT were found to have histopathologic features suggesting malignant potential. SPT with malignant potential should be treated by aggressive resection of the primary tumor and long-term follow-up is needed. Although the prognosis is excellent, careful long-term follow-up is necessary in case of possible tumor recurrence and metastasis in patients with SPT suggesting malignant potential. Twenty per cent of patients with metastasis die after a

mean follow-up of 9.1 years. There have been only few reports of the use of radiotherapy or chemotherapy, so it's difficult to judge the value of such measures.
In conclusion, according to the following guidelines, clinicians and surgeons should: 1) consider the possible disease of SPT in young females, with pancreatic encapsulated lesion with well-defined borders and variable central areas of cystic degeneration, necrosis or hemorrhage showed on radiological examinations. 2) Intensify the differentiation of the clinical symptoms, especially during the course of therapy of chronic gastritis and diabetes. 3) Use immunohistochemical stains of alpha-1-antitrypsin, alpha-1-antichymotrypsin, vimentin and NSE. 4) Keep this unusual but potentially curable tumor in mind, following patients, especially young females, who had suffered from acute pancreatitis or abdominal injury. Increasing experience with this tumour leads to a greater awareness of its clinical presentation and pathological features and a lower rate of misdiagnosis. 5) Finally, perform, where technically feasible, conservative surgical treatment, that is safe and effective.

Riassunto

OBIETTIVO: Il tumore solido pseudopapillare del pancreas (TSPP) è una neoplasia rara. La sua diagnosi preoperatoria è difficile e la terapia risulta spesso inappropriata, causando frequentemente complicanze postoperatorie. Lo scopo di questo lavoro è stato identificare, in base ad una revisione accurata della letteratura, le linee guida per migliorare la diagnosi ed il trattamento del TSPP.
CASO CLINICO: Gli Autori riportano un caso di TSPP insorto in una giovane donna di 27 anni, in cui una erronea diagnosi radiologica ha reso più difficile la strategia chirurgica ed ha quindi causato complicanze postoperatorie.
DISCUSSIONE/CONCLUSIONI: Medici e chirurghi dovrebbero: 1) Considerare la possibilità di diagnosticare il TSPP quando, specialmente in una donna giovane, si evidenzia agli esami radiologici la presenza di una lesione capsulata a bordi ben definiti, con aree centrali di degenerazione cistica, associata ad aspetti necrotici ed emorragici. 2) Intensificare la diagnosi differenziale, specialmente nei pazienti sottoposti a terapia medica per gastrite cronica e diabete. 3) Utilizzare gli studi immunoistochimici per l'alfa-1-antitripsina, l'alfa-1-antichimotripsina, la vimentina e l' enolasi neurone-specifica. 4) Pensare a questa patologia potenzialmente curabile, mentre si seguono pazienti affetti da pancreatite acuta e/o cronica. La maggior esperienza nell'ambito di questi tumori conduce ad una maggior consapevolezza della sua presentazione clinica e quindi ad una minore incidenza di errori diagnostici. 5) Infine, attuare, quando tecnicamente fattibile, un trattamento chirurgico conservativo, che si dimostra sicuro ed efficace.

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