Original Article

Solid pseudopapillary neoplasm of the pancreas in children: a clinical and pathological study of 16 cases

Liling Bao1*, Jiwei Li2*, Mengxing Lv2, Jun Zhou2, Kexuan Qu3, Zijuan Liu4, Yangyang Ma5, Lian Chen5

1Department of Pathology, Kunming Medical University Haiyuan College, Kunming, Yunnan Province, China; Departments of 2Pathology, 3Blood Transfusion, Kunming Children’s Hospital, Kunming, Yunnan Province, China; 4Department of Pathology, The Second Affiliated Hospital of Kunming Medical University, Kunming, Yunnan Province, China; 5Department of Pathology, Fudan University Children’s Hospital, Shanghai, China. *Equal contributors.

Received December 18, 2016; Accepted January 20, 2017; Epub March 1, 2017; Published March 15, 2017

Abstract: Introduction: Solid pseudopapillary neoplasm of the pancreas is an uncommon pancreatic neoplasm with malignant potential. There are many unique differences between children and adults in solid pseudopapillary neoplasm of the pancreas. Our study aimed to illustrate the clinical and pathological features of solid pseudopapillary neoplasm of the pancreas in children. Method: The clinical and pathological data of 16 pediatric cases of solid pseudopapillary neoplasm of the pancreas were retrieved and reviewed from the medical records in the Kunming Children’s Hospital. Results: There were 11 girls and 5 boys, the sex ratio was 2.2:1 (female-to-male); the median age was 9.5 years, and the average age was 9.56±3.65 years (ranging from 3 to 15 years). The chief complaint was abdominal pain (8/16) and a mass in the abdomen (3/16). The median size of the tumors was 7.9 cm in maximum diameter (ranging from 2.8 to 16.4 cm). The lesions were located at the head (7 cases, 43.75%), the body (4 cases, 25%), the tail (1 case, 6.25%), both the head and the body (1 cases, 6.25%), and both the body and the tail (3 cases, 18.75%). 9 cases (including 4 boys) of solid pseudopapillary neoplasm of the pancreas were cystic and solid (56.25%), 6 cases were purely solid (37.5%), and only 1 case was purely cystic (6.25%). Distal pancreatectomy was the choice for the body/tail tumors (50%), pancreaticoduodenectomy and total mass excision for the head tumors (43.75%), and total pancreatectomy for the head and body tumors (6.25%). Histologically, pseudopapillae, solid cell sheets surrounded by fibrovascular stroma, nuclear grooves, areas of myxoid change and haemorrhage were the rudimentary histological patterns of solid pseudopapillary neoplasm of the pancreas. On immunohistochemistry the tumors variably expressed vimentin, neuron-specific enolase, alpha-1-antitrypsin, progesterone receptor, β-catenin, CD99 (dot-like intracytoplasmatic), cytokeratin, synaptophysin, Ki-67 (2-4%), and were negative to chromogranin A. The prognosis was satisfying. The average follow-up was 22.88±16.69 months (ranging from 3 to 61 months) and all the patients were event-free after operation. Conclusion: Solid pseudopapillary neoplasm of the pancreas was a borderline tumor with malignant potential and was uncommon in children. Compared with the adults, the pediatric patients showed many different characteristics: gender disparity, main clinical manifestations, the tumor location distribution, the size and configuration, and degenerative changes. Immunohistochemical markers such as β-catenin and CD99 were useful for the diagnosis. Although with malignant potential, metastases and recurrence were rarely observed in children.

Keywords: Solid pseudopapillary neoplasm of the pancreas, children, pathology, immunohistochemistry

Introduction

Solid pseudopapillary neoplasm of the pancreas (SPNP) is an uncommon pancreatic neoplasm with malignant potential and accounts for 0.13-2.7% of all exocrine pancreatic tumors and about 9-15% of cystic pancreatic tumors [1]. It was first described by Lichtenstein in 1934 [2]. The first case as a mucinous cystic neoplasm of the pancreas was reported by Frantz in 1959 [3, 4]. In 1970 Hamoudi et al. described the ultrastructural features of the tumor which led to its acceptance as a separate clinicopathological entity [5]. Later the World Health Organization designated these tumors as solid pseudopapillary tumors in 1996 [6] and reclassified them as solid pseudopapillary neoplasms in 2010 [7].

SPNP predominantly affected women 40% of which were during the second decade of life, and only approximately 6-8% of SPNP occurred in children [8]. A Korean review showed that there were only 11 pediatric cases in the total...
Solid pseudopapillary neoplasm of the pancreas in children

116 SPNP cases and they had obviously different clinical features compared with adults [9]. Herein, we report a series of 16 cases of SPNP and make a study of their clinical and pathological features with a literature review.

Clinical presentations of SPNP include abdominal pain, palpable abdominal mass, nausea/vomiting, weight loss, jaundice, fever, constipation, diarrhea or fatigue [10]. Most of symptoms are nonspecific [11] and insufficient for diagnosis.

Computed tomography can detect a huge well-encapsulated mass with heterogeneous densities or intensities reflecting degeneration or hemorrhage within classic SPNP [12].

Pathological features are the mainstay for the diagnosis of SPNP. The classic features of SPNP include an evident fibrous capsule and typical pseudopapillary structures. In addition, solid cell sheets surrounded by fibrovascular stroma, nuclear grooves, degeneration and haemorrhage were the auxiliary histological patterns of SPNP [13].

Recently, some of the latest researches suggested that the pediatric patients of SPNP showed different clinical and pathological features compared with adults [14]. Owing to the paucity of SPNP in children, this case series study was conducted to elucidate the clinical and pathological features of SPNP in children.

Materials and methods

Medical records

16 cases of SPNP were retrieved from the medical records in Kunming Children’s Hospital between 1996 and 2015 with the permission of the ethics committee. The data we collected included the sex, age, complaints, lesion size, site, histopathological information, treatment, and follow-up.

Histopathological studies

With pathologic examination, all of the resected pancreatic specimens were fixed in 10% buffered formalin and embedded in paraffin. Block step sections (5 μm) were cut and stained conventionally with haematoxylin and eosin.

Immunohistochemistry

Immunohistochemical staining was performed using the EnVision method. The antibodies were listed in Table 1. Vimentin, Cytokeratin (CK), Synaptophysin (Syn), Chromogranin A (CgA), NSE (Neuron-specific enolase) and α1-AT (Alpha-1-antitrypsin) were expressed in membrane and Ki-67 and progesterone receptor (PR) were positive in nucleus. Particularly, β-catenin was positive in nucleus and cytoplasm, and CD99 showed dot-like intracytoplasmatic positivity.

Results

The clinicopathological data of 16 cases were collected and summarized in Table 2. There were 11 girls and 5 boys, the sex ratio was 2.2:1 (female-to-male); the median age was 9.5 years (ranging from 3 to 15 years), and the average age was 9.56±3.65 years (boys and girls was 8.8±3.7 years and 9.91±3.75 years, respectively). Abdominal pain (8 cases, 50%) and abdominal mass (3 cases, 18.75%) was the chief complaint, and the left (5 cases, 31.25%) were asymptomatic. The median size of tumors was 7.9 cm in maximum diameter (ranging from 2.8 to 16.4 cm). The median size of boys and girls in maximum diameter was 4.8 cm (ranging from 4.0 to 9.6 cm) and 8.0 cm (ranging from 2.8 to 16.4 cm), respectively.

Computed tomography showed that all tumors had clear circumscription and originated from the pancreas (Figure 1). The lesions were located at the head (7 cases, 43.75%), the body (4 cases, 25%), the tail (1 case, 6.25%), both the head and the body (1 cases, 6.25%), and both the body and the tail (3 cases, 18.75%). 9 cases (including 4 boys) of SPNP were cystic.
Table 2. Clinical and pathological features of SPNP in children

<table>
<thead>
<tr>
<th>NO</th>
<th>Sex</th>
<th>Age (year)</th>
<th>Complaints</th>
<th>Size in maximum diameter (cm)</th>
<th>Site</th>
<th>Cut section</th>
<th>Circumscription</th>
<th>Pseudo-papillae</th>
<th>Degeneration</th>
<th>Treatment</th>
<th>Follow-up (months)</th>
<th>Metastasis and Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>3</td>
<td>Asymptomatic</td>
<td>2.8</td>
<td>Head</td>
<td>Solid</td>
<td>Clear</td>
<td>Exist</td>
<td>Hemorrhage, myxoid</td>
<td>TME</td>
<td>54</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>3</td>
<td>Abdominal mass</td>
<td>4.0</td>
<td>Head</td>
<td>Solid And Cystic</td>
<td>Clear</td>
<td>Exist</td>
<td>Hemorrhage, myxoid necrosis</td>
<td>PDD</td>
<td>15</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>6</td>
<td>Abdominal pain</td>
<td>8.0</td>
<td>Body and tail</td>
<td>Solid And Cystic</td>
<td>Clear</td>
<td>Exist</td>
<td>Hemorrhage, myxoid, necrosis</td>
<td>DP</td>
<td>28</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>7</td>
<td>Asymptomatic</td>
<td>10.2</td>
<td>Head</td>
<td>Solid</td>
<td>Clear</td>
<td>Exist</td>
<td>Hemorrhage, myxoid</td>
<td>PDD</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>8</td>
<td>Abdominal pain</td>
<td>9.6</td>
<td>Body</td>
<td>Solid And Cystic</td>
<td>Clear</td>
<td>Exist</td>
<td>Hemorrhage, myxoid</td>
<td>DP</td>
<td>12</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>8</td>
<td>Asymptomatic</td>
<td>9.5</td>
<td>Head</td>
<td>Solid</td>
<td>Clear</td>
<td>Exist</td>
<td>Hemorrhage, myxoid, necrosis</td>
<td>PDD</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>9</td>
<td>Asymptomatic</td>
<td>8.9</td>
<td>Body</td>
<td>Solid</td>
<td>Clear</td>
<td>Exist</td>
<td>Hemorrhage, myxoid</td>
<td>DP</td>
<td>36</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>9</td>
<td>Abdominal pain</td>
<td>4.8</td>
<td>Body</td>
<td>Solid And Cystic</td>
<td>Clear</td>
<td>Exist</td>
<td>Hemorrhage, myxoid</td>
<td>DP</td>
<td>32</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>10</td>
<td>Abdominal mass</td>
<td>6.0</td>
<td>tail</td>
<td>Solid And Cystic</td>
<td>Clear</td>
<td>Exist</td>
<td>Hemorrhage, myxoid, necrosis</td>
<td>DP</td>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>11</td>
<td>Abdominal pain</td>
<td>7.8</td>
<td>Head</td>
<td>Solid And Cystic</td>
<td>Well demarcated</td>
<td>Exist</td>
<td>Hemorrhage, myxoid, necrosis</td>
<td>PDD</td>
<td>61</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>12</td>
<td>Abdominal mass</td>
<td>8.2</td>
<td>Head</td>
<td>Solid</td>
<td>Clear</td>
<td>Exist</td>
<td>Hemorrhage, myxoid</td>
<td>PDD</td>
<td>25</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>12</td>
<td>Abdominal pain</td>
<td>5.5</td>
<td>Head</td>
<td>Cystic</td>
<td>Clear</td>
<td>Exist</td>
<td>Hemorrhage, myxoid, necrosis</td>
<td>PDD</td>
<td>8</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>12</td>
<td>Abdominal pain</td>
<td>5.0</td>
<td>Body and tail</td>
<td>Solid And Cystic</td>
<td>Clear</td>
<td>Exist</td>
<td>Hemorrhage, myxoid, necrosis</td>
<td>DP</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>14</td>
<td>Asymptomatic</td>
<td>6.8</td>
<td>Body</td>
<td>Solid</td>
<td>Well demarcated</td>
<td>Exist</td>
<td>Hemorrhage, myxoid</td>
<td>DP</td>
<td>15</td>
<td>No</td>
</tr>
<tr>
<td>15</td>
<td>F</td>
<td>14</td>
<td>Abdominal pain</td>
<td>8.5</td>
<td>Body and tail</td>
<td>Solid And Cystic</td>
<td>Clear</td>
<td>Exist</td>
<td>Hemorrhage, myxoid</td>
<td>DP</td>
<td>22</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>F</td>
<td>15</td>
<td>Abdominal pain</td>
<td>16.4</td>
<td>Head and body</td>
<td>Solid And Cystic</td>
<td>Clear</td>
<td>Exist</td>
<td>Hemorrhage, myxoid, hyaloid</td>
<td>TP</td>
<td>28</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: F, female; M, male; DP, distal pancreatectomy; PDD, pancreaticoduodenectomy; TME, total mass excision; TP, total pancreatectomy.
Solid pseudopapillary neoplasm of the pancreas in children

and solid (56.25%), 6 cases were purely solid (37.5%), and only 1 case was purely cystic (6.25%).

Distal pancreatectomy was the choice for the body/tail tumors (50%), pancreaticoduodenectomy and total mass excision for the head tumors (43.75%), and total pancreatectomy for the head and body tumors (6.25%).

Histologically, all the tumors were well-circumscribed with a fibrotic pseudocapsule. Monomorphic tumor cells were polygonal or oval with prominent pink or hyaline cytoplasm (Figure 2A) and some eosinophilic globules could be detected in or outside the cytoplasm (Figure 2B). Most tumor cells arranged around the blood vessels in a pseudopapillary pattern (Figure 2C) or in sheets with thin fibrovascular septa (Figure 2D). Some tumor cells displayed just like the pseudorosettes (Figure 2E). Large areas of cellular cystic degeneration (Figure 2F), hemorrhage (Figure 2G), and necrosis (Figure 2H) were highlighted. Pseudoglandular pattern with hyalinized collagenous stroma was observed partially (Figure 2H). Cellular mitosis was not observed.

On immunohistochemistry the tumor cells variably expressed vimentin, NSE, α1-AT, PR, CK and Syn, and did not express CgA. The characteristic markers of SPNP were CD99 and β-catenin. β-catenin was positive in nucleus and cytoplasm, and CD99 was dot-like intracytoplasmatic. Ki-67 index was 2-4% (Figure 3).

The prognosis of our patients was satisfying. The average follow-up was 22.88±16.69 months (ranging from 3 to 61 months), and all the patients were event-free after operation.

Discussion

To date, about 1000 cases of SPNP have been reported, and more than two-thirds of them appeared in the last 10 years [15, 16]. This probably reflected the increasing awareness of the clinicopathologic and radiographic features of SPNP and the uniformity of the nomenclature used for SPNP. However, the etiology and the differentiation status of SPNP remained challenging and still enigmatic [17].

Although the age of patients ranged widely from 2 to 85 years, SPNP mainly affected women during the second decade of life [18]. The largest reported pediatric case series showed the median age was 11.2 years [19], and our patient’s median age of 9.5 years was lower than it. The sex ratio (female-to-male) was 9.78:1 in adults [20], and 3:1 [21] or 4.5:1 [22] in children. Our sex ratio of 2.2:1 (female-to-male) was lower than the previously reported in children, which suggested a lower female preponderance of SPNP in children in accord with Jung’s report [23].

The common clinical manifestation of SPNP was abdominal pain and mass. Allison L. Speer reported most of 11 pediatric cases presented with abdominal pain (73%) [24]. Some literatures [25] demonstrated a significant difference in symptoms between adults and children in their comparative study. Although in adults it most commonly manifested as an incidental finding (38.3%) followed by abdominal pain (34%), SPNP in children most frequently presented with abdominal pain and a palpable mass [26]. The abdominal pain (50%) and abdominal mass (18.75%) was the chief complaint in our study which was also confirmed by other studies.

There were 8 cases at head (50%) which was similar to the literature in children (66.7% head) [27], but different from adults (80.9% body or tail) [28]. The median size of our tumors was 7.9 cm (ranging from 2.8 to 16.4 cm) in maximum diameter, and the size of girls was larger than that of boys (8.0 cm vs. 4.8 cm) similar to the previous study [29]. Lee et al. [30] demonstrated that the size in children was significant-
Solid pseudopapillary neoplasm of the pancreas in children

Figure 2. (A) The tumor cells were uniform with plenty of cytoplasm (×100). (B-D) Eosinophilic globules (B, ×400), pseudopapillary pattern (C, ×100) and thin fibrovascular septa (D, ×200) was highlighted. (E) Elongated tumor cells radiated around blood vessels and were similar to pseudorosettes in ependymoma (×400). (F, G) Cystic degeneration (F, ×100), hemorrhage (G, ×50), and necrosis (G, ×50) was shown. (H) There was obvious pseudoglandular structure and hyalinized collagenous stroma (×100).

Figure 3. (A-C) Vimentin (A, ×200), α1-AT (B, ×400) and PR (C, ×400) was diffusely positive in tumor cells. (D) β-catenin showed unique positivity in nucleus and cytoplasm (×200). (E) CD99 was dot-like intracytoplasmatic (×400). (F) The Ki-67 index was about 2-4% (×400).

ly larger than that in adults (7.1 cm vs. 4.9 cm), and the bigger tumors easily occurred hemorrhage and/or myxoid, which gave rise to cystic spaces, ischemia and degenerations.
Solid pseudopapillary neoplasm of the pancreas in children

Histologically, all of our cases were macroscopically large and well encapsulated by a fibrous capsule. The tumor cells appeared pseudopapillaes, solid sheets surrounded by fibrovascular stroma, nuclear grooves, and areas of degeneration change, which were in accord with the rudimentary histological patterns of SPNP [31, 32]. Degenerative cysts, haemorrhage, necrosis and myxoid areas were common [33, 34]. According to the previous literatures, many studies found that SPNP in women showed cystic or degenerative changes and grew rapidly in early stage. Compared to women, SPNP in men were more likely to occur as a solid mass and to degenerate less frequently and more slowly during their growth [35-37]. Nishihara et al. reached almost the same conclusion and found that the mean age of men with degeneration in SPNP was higher than that of women (31.4 vs. 25.5 years) [38]. However, some researchers reported that the degenerative changes have no obvious gender discrepancy in pediatric SPNP [39]. Most of our cases were cystic and solid (56.25%) including 4 boys (80% of male) and 5 girls (45.45% of female). Small case number in our study might be the explanation for the high degeneration rate in boys.

Non-specific immunohistochemical markers were discovered in SPNP. The tumor cells variably expressed Vimentin, NSE, α1-AT, PR, CK and Syn but did not express CgA [40]. β-catenin and CD99 may be helpful in the diagnosis of SPNP for their unique pattern. β-catenin was positive in nucleus and cytoplasm, and CD99 showed dot-like intracytoplasmatic expression. According to the recent studies, almost SPNP had active mutations of the β-catenin (CTNNB1) gene, and expressed β-catenin in a diffuse cytoplasmic and aberrant nuclear pattern, which was accompanied by a lack of membranous E-cadherin [41, 42]. Except for some acinar cell carcinoma of the pancreas and pancreatoblastoma, pancreatic neuroendocrine tumor (PET) consistently lacks the nuclear expression of β-catenin. Thus, β-catenin was specific for SPNP [43]. Our patients’ immunoprofiles were consistent with previous studies. Recently published data showed that a particular dot-like intracytoplasmatic expression of CD99 appeared to be highly unique for SPNP [44]. CD99 was a glycoprotein encoded by the pseudoautosomal gene MIC2, and was expressed in the cellular membrane of Ewing sarcoma (ES), primitive neuroectodermal tumor (PNET), lymphoblastic lymphoma, synovial sarcoma and other solid tumors [45]. The characteristic cytoplasmatic paranuclear “dot-like” pattern described in SPNP had also been found in colonic adenomas/adenocarcinomas, pituicytomomas and endometrial serous carcinomas with ES differentiation, but to date it was rarely described in other types of endocrine or exocrine pancreatic tumors included in the differential diagnosis of SPNP [46]. The pseudopapillary regions of all our samples displayed the distinctive CD99 staining pattern which was consistent with previous reports. Some studies suggested that sex hormones might be involved in the origin of the tumor [47]. Many researchers found that the tumor cells in SPNP always expressed PR, but did not express estrogen receptor and/or androgen receptor [40]. Hence, some scholars proposed that no differences in immunohistochemical stains for sex hormone receptors in clinicopathological characteristics had been found attributable to gender alone [39]. Ki-67 index was about 2-4% in our studies suggesting the proliferative activity of the tumor cells was low.

Pancreatoblastoma, PET, acinar cell carcinoma of the pancreas, and ductal adenocarcinoma of pancreas should come to the differential diagnosis of SPNP. Pancreatoblastoma usually affects children younger than 10 years and has no female predilection. It is more aggressive than SPNP, and usually has liver metastasis [48]. Histologically, it shows clusters of primitive polygonal cells with hypercellular stroma and the characteristic squamoid corpuscles. PET has characteristic morphological features, such as solid monomorphous growth pattern and rosette-like structures. In addition, it also expresses neuroendocrine markers, such as Syn, NSE, and CD56 [49]. Acinar cell carcinoma of the pancreas is manignant and usually occurs in adults. It has uniform tumor cells arranged in solid and acinar pattern. The expression of pancreatic enzymes such as trypsin, chymotrypsin, and lipase may be useful. Ductal adenocarcinoma of pancreas is a malignant epithelial carcinoma exclusively seen in adults. It has an unique expression of a cytokeratin antibody panel.

Complete surgical resection is very effective for SPNP. Distal pancreatectomy, pancreaticoduodenectomy, total mass excision and pancreatotomy was the treatment for the tumors in the different sites respectively [50-52]. Our patients also received the different surgical
procedure according to the different location. Routine lymphadenectomy was not recommended due to the rare incidence of metastasis [53, 54].

The overall 5-year survival rate of SPNP was about 95% [55]. Approximately 10-15% of SPNP patients developed metastasis [53, 54]. Predicting aggressive behavior was still challenging because there were no reliable prognostic factors [57]. Our follow-up was satisfying and all the patients were alive without events. Metastases and recurrence were not observed in our study.

Conclusion

SPNP is an uncommon pancreatic neoplasm in children. The presentations of SPNP in children are different from those of adults. They have many unique features: the patients lack relatively obvious gender ratio; abdominal pain and abdominal symptoms are main clinical manifestations; the tumors frequently locate at the head and body; the size and configuration of tumors lack obvious gender difference; most tumors are composed of cystic and solid configurations, and degenerative changes occur earlier in tumor growth.

In summary, we report 16 pediatric SPNP and make a preliminary clinicopathological study. More data are needed to promote the progressive realization and diagnosis of SPNP in children.

Disclosure of conflict of interest

None.

Address correspondence to: Drs. Yangyang Ma and Lian Chen, Department of Pathology, Children’s Hospital of Fudan University, Shanghai, China. Tel: (86) 21-6493-1728; Fax: (86) 21-6493-1914; E-mail: mashi441300@163.com (YYM); doctchenlian@163.com (LC)

References

Solid pseudopapillary neoplasm of the pancreas in children


