Pancreatoblastoma

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Summary

Pancreatoblastoma (PB), or infantile pancreatic carcinoma, is an extremely rare pancreatic tumor in childhood, comprising 0.5% of pancreatic non-endocrine tumors. Although PB mainly presents during childhood but can also occur in adults. PB tend to be less aggressive in infants and children compared to adults. Children with PB usually present late with upper abdominal pain and many have a palpable mass in the epigastrium. Mechanical obstruction of the upper duodenum and gastric outlet by tumor in the head of the pancreas may be associated with vomiting, jaundice and gastrointestinal bleeding. Histologically, PB is characterized with distinct acinar and squamoid cell differentiation. PB has been associated with alterations in the Wnt signaling pathway and chromosome 11p loss of heterozygosity (LOH), Beckwith-Wiedemann syndrome and familial adenomatous polyposis. The majority of these tumors arise in the head of the pancreas. Alpha-fetoprotein may be elevated in up to 68% of patients with PB. Ultrasound and CT scan may be useful but preoperative diagnosis is often quite difficult. The treatment of choice is complete resection, that may often be curative. The role of adjuvant chemotherapy or radiotherapy is still under discussion due to small number of patients treated as yet. Chemotherapy regimens consisting of cyclophosphamide, etoposide, doxorubicin, and cisplatin have been used in neoadjuvant setting with anecdotal benefit. Prognosis of this rare tumor is good, when resected completely. Prognosis is poorer, when there is metastasis or when it is inoperable. On the whole, PB is regarded to be a curable tumor; hence the clinical diagnosis should be made early. Awareness of this rare tumor of pancreas is essential for early detection and proper management. The author review the clinical presentation, etiology, diagnosis, treatment and prognosis of PB in this presentation.
Pancreatoblastoma (PB), is an extremely rare pancreatic tumor of childhood, but can occur in adults. PB often exhibits elevated plasma levels of alpha-fetoprotein. PB, though not common, is said to be less aggressive in infants and children compared to adults [2, 3, 4].

**Definitions and Disease Name**

- PB (PB) is an extremely rare pancreatic tumor of childhood.
- The term PB was coined in 1977 and has subsequently been employed to describe tumors previously known as “infantile carcinoma of the pancreas” [5].
- PB has several similarities to hepatoblastoma, a tumor found in an identical age group with a closely related morphological appearance [6]:
  - both tumors occur in association with the Beckwith-Wiedemann syndrome;
  - both often exhibit elevated plasma levels of AFP;
- PB associated with Beckwith-Wiedemann syndrome all occurred in newborns, 86% in males. This similarity may lead to diagnostic confusion as tumor origin cannot always be accurately determined on CT scanning.

PB is an extremely rare pancreatic tumor of childhood. The term PB was coined by Horie et al. in 1977 to describe tumors previously known as “infantile carcinoma of the pancreas” [5]. PB has several similarities to hepatoblastoma, including association with the Beckwith-Wiedemann syndrome and elevated plasma levels of alpha-fetoprotein (AFP) [6].

**Epidemiology**

- PB is an extremely rare pancreatic tumor in childhood, comprising 0.3% of pancreatic non-endocrine tumors [2].
- Approximately 200 cases in children, and less than 20 cases in adults, have been reported in the literature.
- Median (range) age at presentation is 5 (range 0-68) years [7].
- PB have been diagnosed in-utero as well as in adults, with the oldest patient being 68-year-old.
- Male : female ratio is 1.14:1.
- It is thought to be more common in Asians than Whites [8].
- Median survival rate is near 48 months [9].
- 5-year survival rate is approximately 50% (range 37.62%) [9].
- More than 15% of patients present with metastases at the time of diagnosis, the liver being the commonest site (more than 80%).
- Skeletal metastases have also been reported.

Pancreatic tumors are rare in children, and PB comprises only 0.5% of pancreatic non-endocrine tumors occurring in children. This tumor is more common in Asians than in the white population. They have also been diagnosed in-utero and in adults, with the oldest patient being 68-year-old. [2, 7, 8, 9]

**Gross Pathology**

- **Location [3]:**
  - Most frequent site is the head of pancreas (approximately 39%).
  - Poorer prognosis if the tumor is situated in body or tail as it is difficult to resect, and hence, there are more chances of recurrence.
- **Size [3]:**
  - PB measuring up to 25x20x15 cm and weighing up to 2.5 kg have been reported.
- **Capsule [1]:**
  - Majority of PB are encapsulated, while the rest are partially encapsulated.
  - Encapsulated tumors have a better prognosis.

Largest size reported in the literature reviews has been around 15 cm. Majority of the tumors are encapsulated, while the rest are partially encapsulated. Encapsulated tumors have a better prognosis. [1, 3]
The specimen photograph shows an encapsulated tumor with a nodular surface. The capsule is complete [1].

**Etiology**

- **Wnt signaling pathway**: alterations in the Wnt signaling pathway and chromosome 11p loss of heterozygosity (LOH) [6].
- **Beckwith-Wiedemann syndrome**: molecular association between PB and other embryonal tumors, such as hepatoblastoma and Wilms' tumor, has been previously suggested by the presentation of Beckwith-Wiedemann in children with these tumors [6, 11, 12].
- **Familial adenomatous polyposis**: has been associated with PB [13].

Molecular investigation has disclosed a mosaic paternal 11p15 uniparental disomy in the tumor cells of PB. Recently genetic alterations also have been characterized and the commonest change is allelic loss of 11p. Familial adenomatous polyposis and Beckwith-Wiedemann syndrome have also been associated with PB [6, 10, 11, 12, 13].

**Histogenesis**

- Histogenesis of PB is still uncertain [14].
- It is believed to be hamartomatous or dysembryogenic development of ductal cells of ventral portion of primordial pancreas.
- PB contains pluripotent cells capable of differentiating along the pathway of all three pancreatic cell types.

PB can exhibit acinar, endocrine and ductal differentiation. Histopathological features that are readily seen include hemorrhage, capsule formation and necrosis. [14, 15, 16]

**Immunohistochemistry** [15, 16]

- Immunohistochemistry is usually strongly positive for alpha-1-antitrypsin and glucose-6-phosphatase, in addition acid phosphatase, esterase and enteroprotease activity may be demonstrated using histochemistry.
- Stains for chromogranin, synaptophysin and neuron-specific enolase are often positive.
- Trypsin and chymotrypsin are usually found in acinar regions but positivity for specific peptide hormones is rare.
- Immunohistochemistry for AFP may be positive within solid regions of the epithelial component.
- Electron microscopy reveals multiple cytoplasmic neurosecretory zymogen granules.
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The tumor cells show strong positive immune reaction for trypsin (A), alpha1-antitrypsin (B), alpha1-antichymotrypsin (C), and CA 19-9 (D). Note that the luminal contents are positive for alpha1-antitrypsin (B), alpha1-antichymotrypsin (C), and CA 19-9 (D) (original magnifications x400) [17].

Biochemistry and radiology are the main diagnostic tools in PB.

### Serum Tumor Markers
- There is no clear role of serum tumor markers in PB.
- PB often exhibits an elevated serum AFP level but a case report of a patient with no elevation of serum AFP, but positive AFP immunohistochemistry, has been reported [4, 18].
- Utility of CA 19-9, lipase, trypsin, chymotrypsin, alpha-amylase, or chromogranin is unclear as well [19].
- Serum LDH levels may be elevated in a minority of cases [2].

### Alpha-Fetoprotein (AFP) [4, 18]
- Elevated AFP may be an indicator of PB.
  - This is due to the fact that both the liver and the pancreas arise from the same primitive cells, and the regression associated with neoplastic cells is similar in both organs.
- Immunohistochemistry for AFP may be positive within solid regions of the epithelial component, and help diagnosis.
- Elevated in approximately 68% of cases of PB.
- Can be used as an indicator to response to chemotherapies in neoadjuvant setting.

Elevated serum AFP levels have been reported in up 68% of cases. AFP level comes down once the tumor is resected. [4, 18]

### Radiological Imaging [7, 8, 14]
- Ultrasound, CT scan, and MRI may be useful but preoperative diagnosis is often quite difficult.
- Imaging may show a finely calcified mass in the region of the pancreas that may be reminiscent of neuroblastoma.
  - Calcifications are generally not large or formed, as is seen in teratoma.
- PB are often large at diagnosis with hemorrhagic necrosis and degeneration within the tumor.
  - Both solid and cystic elements are typically present.
- Metastases to liver and lymph nodes are common at diagnosis; lung and brain metastases are rarer.

Radiological staging include a CT scan of abdomen, pelvis and chest. Bone scan or a brain MRI may be performed if clinically indicated. [2, 7, 8, 14]
Enhanced axial CT image shows a large well-defined cystic tumor in the tail of pancreas and multiple small nodules in the liver [1].

**Differential Diagnosis (1)**

- The most common cystic pancreatic neoplasms in children are microcystic adenomas and cystadenocarcinomas.
- Their appearance is similar to that in adults.
- They may cause a pseudocystic peri toneum if they rupture into the peritoneum.

The most common cystic pancreatic tumors in children are microcystic adenomas and cystadenocarcinomas.

**Differential Diagnosis (2)**

Pancreatic tumors in children are classified as epithelial (non-endocrine and endocrine) and non-epithelial in origin.

**Non-epithelial tumors**

-Primary hyperplastic, pleomorphic neuroendocrine tumor (PHEO) and benign, or metastatic lymph nodes in the mesentery and mesocolon.

**Benign non-endocrine: adenoma and dermoid cyst (benign).**

**Endocrine:** neurofibromas and melanomas.

**Most common cystic pancreatic neoplasms:** microcystic adenoma and cystadenocarcinoma. Their appearance is similar to that in adults. They may cause a pseudocystic peri toneum if they rupture into the peritoneum.

Differentiation of PB from other tumors is extremely important as prognosis of this rare tumor is good, when resected completely.

**Clinical and Biologic (2)**

- Insulinoma: hypoglycemia, behavior change, weight gain and/or morning seizures;
- Gastrinoma: severe gastrointestinal ulceration and diarrhea;
- VIPoma: watery diarrhea, hyperkalemia and achlorhydria;
- Glucagonomas: migratory necrotic dermatitis, weight loss, stomatitis, anemia and hyperglycemia;
- Somatostatinomas: diarrhea and may develop diabetes mellitus.

**Staging [70]**

- The tumor, node, metastasis (TNM) classification of the American Joint Committee on Cancer is usually used to determine the tumor staging.

**TNM Staging**

- **Primary tumor (T)**
  - TX: Primary tumor cannot be assessed
  - T0: No evidence of primary tumor
  - Tis: Carcinoma in situ
  - T1: Tumor limited to the pancreas, ≤2 cm in greatest dimension
  - T2: Tumor limited to the pancreas, >2 cm in greatest dimension
  - T3: Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
  - T4: Tumor involves the celiac axis or the superior mesenteric artery (inseparable from primary tumor)

- **Regional lymph nodes (N)**
  - NX: Regional lymph nodes cannot be assessed
  - N0: No regional lymph node metastasis
  - N1: Regional lymph node metastasis

- **Distant metastasis (M)**
  - MX: Distant metastasis cannot be assessed
  - M0: No distant metastasis
  - M1: Distant metastasis
The tumor, node, metastasis (TNM) classification of the American Joint Committee on Cancer is usually used to determine the tumor staging [20].

PB is less aggressive in infants and children compared to adults. Prognosis of PB is good, when resected completely. Prognosis is poorer, when there is metastasis or when it is inoperable. [2, 7, 21]

**Prognosis** [7, 21]

- Outcome of PB is generally favorable in pediatric patients without metastasis.
- Overall survival is at least 80% in children with completely resectable PB at diagnosis.
- Pediatric patients with metastasis have poor outcome with median survival of 1.5 years.

**Prognostic Factors** [7]

- Data:
  - 153 patients with PB identified from MEDLINE and combined with patients identified from the Royal Liverpool University Hospital.
- Results:
  - On univariate analysis, factors associated with a worse prognosis were synchronous (P<0.001) or metachronous metastases (P=0.001), non-resectable disease at presentation (P=0.001) and age >16 years at time of presentation (P=0.02).
  - On multivariate analysis, resection (P=0.006) and metastases post-resection (P=0.001), but not local recurrence, influenced survival.

**Stage Grouping**

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1-2</td>
<td>0</td>
<td>0</td>
<td>Tumor confined to pancreas: ≤2 cm; A1 ≥2 cm B</td>
</tr>
<tr>
<td>II</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery (A) or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>Regional lymph-node involvement (B)</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>any</td>
<td>0</td>
<td>Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)</td>
</tr>
<tr>
<td>IV</td>
<td>any</td>
<td>any</td>
<td>1</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>

**Treatment**

I. Treatment of choice is complete resection with long-term follow-up aiming to treat any early local recurrence or metastasis.

II. If the tumor is unresectable, then it is recommended that PB is treated in accordance with chemotherapy regimen.

III. Role of radiotherapy is unknown but consideration is appropriate when recurrence has occurred following previous surgery and patients with incomplete resection.

PB has an indolent course and is amenable for various modes of treatment but surgery is the most optimal treatment.

**Surgery (1)** [1, 2, 3, 7, 8, 9, 22]

- Initial management requires an open biopsy and/or where feasible complete surgical resection.
  - Primary surgery should not involve a microscopic residual, so if this is likely to occur, biopsy only should be performed.
  - Whilst tumors involving the head of the pancreas, including those infiltrating the duodenum may be operable, a number of features are inconsistent with primary resection.
  - Infiltration of the porta hepatic including one or more of the following: portal vein and hepatic artery.
  - Involvement of surrounding major vessels such as the aorta, inferior vena cava or celiac axis.

**Surgery (2)**

- The treatment of choice is complete resection, that may often be curative.
  - This approach is consistent with case reports described in the literature and incorporates a treatment plan which will be familiar to most pediatric oncology centers.
  - Published evidence suggests that as in the case of hepatoblastoma, macroscopic surgical resection is important for cure.
  - The long-term prognosis after complete resection is good, but a long-term follow-up is warranted as recurrence is common.
  - Most of data in treatment of PB is anecdotal.
  - The role of adjuvant chemotherapy or radiotherapy is still not clear due to small number of patients treated as yet.

Complete resection of the tumor offers the best prognosis. However, in the presence of metastatic disease, it is of limited value. [1, 2, 3, 7, 8, 9, 22]
In these situations where there are suspected or documented metastatic lesions, empirical chemotherapy regimens that include cisplatin and doxorubicin have been used. A higher rate of metachronous metastasis has been reported in patients undergoing chemotherapy. [1, 2, 3, 7, 8, 9, 23, 24, 25, 26]

Radiotherapy [27]

The role of radiotherapy is unknown but consideration is appropriate where recurrence has occurred following previous surgery and chemotherapy.

Radiotherapy may be indicated for either a persistently unresectable tumor of following grossly incomplete resection or microscopic disease but is usually reserved for relapse.

When the tumor is unresectable and the patient is non-responsive to chemotherapy, radiotherapy is given. Shrinkage of PB has been reported after treatment with radiotherapy [27].

PB in Adults [8, 16, 17]

PB is an even rarer entity in adult population.

Among adult cases that were reported, an age range of 19 to 78 years is reported with male:female ratio of 1:1.3.

PB shows no preferential location adults, but the most frequent site was the head of pancreas (up to 39%) in pediatric cases.

The prognosis of PB in adult population is poor.

Adults with PB have a median survival time of approximately 10 months.

Greater than 50% of adult patients reported died of PB in less than 3 years.

[8, 16, 17]
Many Unanswered Questions?

- What is the role of radiotherapy?
- What is the role of chemotherapy in pancreatic tumors and what is the optimum regimen?
- Does primary chemotherapy reduce surgical morbidity and mortality?
- Does chemotherapy reduce the risk of recurrence following marginal excision?
- Are metastatic PB curable?

Conclusions

- PB is an extremely rare and distinctive malignancy in adult population.
- Unlike in pediatric population where prognosis is good especially when the disease is resectable, PB in adults bear poor prognosis particularly when there is metastasis or when it is inoperable.
- Owing to its rarity, the treatment approach to adult patients with PB is far from being standardized.
- Awareness of this entity and its various modes of presentation will allow us to make early diagnosis of this unusual malignancy, thereby enabling us to learn more of its biology, and ultimately to formulate more systematic approach toward PB.

Received September 9th, 2006 - Accepted September 23rd, 2006

Keywords alpha-Fetoproteins; Beckwith-Wiedemann Syndrome; Cisplatin; Doxorubicin; Hepatoblastoma; Infant; Pancreatic Neoplasms

Abbreviations LOH: loss of heterozygosity; PB: pancreatoblastoma

Acknowledgements We thank Dr. Naik [1] and Dr. Shabaik [17] for allowing us to reproduce figures from their publications. The figures have been reprinted with permission from: Singapore Medical Journal (SMJ), Copyright® 2006 by the Singapore Medical Association [1]; and Archives of Pathology and Laboratory Medicine, Copyright® 2006 by the College of American Pathologists [17]

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Document URL: http://www.joplink.net/prev/200701/08.html


