Pancreatoblastoma

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1Adapted from “Guidelines for the investigation and management of Pancreatoblastoma”, a publication from The United Kingdom Children’s Cancer Study Group (UKCCSG) http://www.ukccsg.org/

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Abstract

Pancreatoblastoma is an extremely rare pancreatic tumor in childhood. Children with pancreatoblastoma 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 haemorrhaging. Poor nutritional intake and the resultant weight loss may also be found. Preoperative imaging with US, CT and/or MRI will usually suggest a correct diagnosis of pancreatoblastoma. Serum alpha-fetoprotein (AFP) levels often provide a useful marker of tumor response and may be predictive of chemoresponsiveness. Serum lactate dehydrogenase (LDH) levels may be elevated in a minority of cases. Initial management requires an open biopsy and/or where feasible complete surgical resection. Responses to chemotherapy varies among reported cases. Local radiotherapy is recommended where there is evidence of micro- or macroscopic residue but is usually reserved for relapse. Overall survival is at least 80% in children with completely resectable tumors at diagnosis. By contrast the outlook for children with metastatic disease, usually hepatic or skeletal, is very poor.

Key-words

Pancreatoblastoma, Beckwith-Wiedemann syndrome, pancreatic tumor, AFP, LDH, PLADO chemotherapy

Definition and disease name

Pancreatoblastoma is an extremely rare pancreatic tumor in childhood. The term pancreatoblastoma was coined in 1977 and has subsequently been employed to describe tumors previously known as “infantile carcinoma of the pancreas” (Horie et al, 1977).

Excluded diseases

Pancreatoblastoma has several similarities to hepatoblastoma, a tumor found in an identical age group with a closely related morphological appearance. Both tumors occur in association with the Beckwith-Wiedemann syndrome (Drut & Jones, 1988, Koh et al, 1986; Kerr et al, 2002) and often exhibit elevated plasma levels of
alpha-fetoprotein (AFP) (Moroshi et al, 1990; Morgan et al, 1996). The cases of pancreaticoblastoma 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.

**Differential diagnosis**
Clinically pancreaticoblastoma can be distinguished from the following neuroendocrine tumors due to their different spectrum of symptoms:
- Insulinoma: hypoglycemia, behavior change, weight gain and/or morning seizures.
- Gastrinoma: severe gastrointestinal ulceration and diarrhea.
- VIPoma: watery diarrhea, hyperkalemic and achlorhydria.
- Glucagonomas: migratory necrolytic dermatitis, weight loss, stomatitis, anemia and hyperglycemia.
- Somatostatinomas: diarrhea and may develop diabetes mellitus.

**Incidence**
From 1971 to 2000, 41 cases of pancreatic tumors were reported to the UK National Registry of Childhood Tumors (Table 1; Charles Stiller, personal communication). Of this total, 25 were malignant of which 11 were pancreaticoblastomas. In order of frequency these were pancreaticoblastoma, islet cell tumors, papillary-cystic neoplasm and adenocarcinoma. Comparable information is not available from either the US (Giulio D’Angio, personal communication) or the International Society of Pediatric Oncology.

**Table 1: Pancreatic tumors reported to the UK National Registry of Childhood Tumors, 1971-2000**

<table>
<thead>
<tr>
<th>Histological Classification</th>
<th>Number</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>(i) malignant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatoblastoma</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Islet cell carcinoma</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Malignant carcinoid</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other (NHL, sarcoma, neuroblastoma, yolk sac tumor)</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>(ii) non-malignant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papillary cystic neoplasm</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>Islet cell tumor</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Cystadenoma</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Acinic cell tumor</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

**Clinical description**
Children with pancreaticoblastoma 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 hemorrhaging. Poor nutritional intake and the resultant weight loss may also be found.

**Histopathology**
Histologically, pancreaticoblastoma exhibits dense cellularity with acinar differentiation and characteristic “squamoid corpuscles”. Both cystic change and calcification have been described within individual tumors. Most cases are formed of an epithelial component (usually predominant) separated into distinct lobules by fibrous stroma. The epithelial component usually consists of distinct acini, solid sheets and “squamoid corpuscles”. Eosinophilic cells with zymogen-type granules may be present and there may be teratoid differentiation into cartilage, bone, osteoid or spindle cells. Squamous, glandular and undifferentiated elements may be intermingled in an organoid fashion. 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 (Kissane et al, 1994; Klimstra et al, 1995).
Staging
The tumor, node, metastasis (TNM) classification of the American Joint Committee on Cancer (Fleming et al., 1997) (Table 2) is usually used to determine the tumor staging (Table 3).

Table 2: Definition of TNM

**Primary Tumor (T)**
- TX: Primary tumor cannot be assessed
- TO: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor limited to the pancreas 2 cm or less in greatest dimension
- T2: Tumor limited to the pancreas more than 2 cm in greatest dimension
- T3: Tumor extends directly into any of the following: duodenum, bile duct, peripancreatic tissues
- T4: Tumor extends directly into any of the following: stomach, spleen, colon, adjacent large vessels

**Regional Lymph Nodes (N)**
- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis
  - pN1a: Metastasis in a single regional lymph node
  - pN1b: Metastasis in multiple regional lymph nodes

**Distant Metastasis (M)**
- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

Table 3: Stage grouping

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

**Chemotherapy**
If the tumor is unresectable, then in view of the many similarities between pancreatoblastoma and hepatoblastoma, it is recommended that pancreatoblastoma is treated in accordance with SIOPPEL 3, i.e. the PLADO chemotherapy arm. 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. Radiotherapy may be indicated for either a persistently unresectable tumor or following grossly incomplete resection or microscopic disease but is usually reserved for relapse. Primary surgery should not leave microscopic residue, so if this is likely to occur, biopsy only should be performed.

Patients with pancreatoblastoma who are completely resected at presentation - Stage I - with normalization of circulating AFP receive six courses of PLADO chemotherapy. All other stages also receive a total of six courses of PLADO chemotherapy but where biopsy only has occurred at diagnosis, surgical excision should be considered when clinically appropriate after at least two courses of PLADO. Children with either static or progressive disease at any time during treatment should immediately undergo an attempt at radical resection. Long term survival has not been reported following disease progression during first line treatment. Second line chemotherapy with ifosfamide, carboplatin and etoposide (ICE) may be given if renal function is adequate, otherwise a combination of vincristine, actinomycin D and cyclophosphamide is suggested. PLADO chemotherapy consists of:

- Day 1: Cisplatinum (PLA) 80 mg/m²/day in continuous I.V. infusion for 24 hours
- Day 2: Doxorubicin (DO) 30 mg/m²/day in continuous I.V. infusion for 48 hours, i.e. total of 60 mg/m²/course.

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

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Diagnostic methods

Biochemistry
- AFP
- LDH

Radiology
- Ultrasound abdomen
- CT scan abdomen plus contrast (MRI scan maybe helpful)
- CT scan chest
- Bone scan

Unresolved 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 pancreatoblastomas curable?

Some of these questions maybe resolved in the forthcoming study SIOP PBL under the auspices of SIOPPEL International Paediatric Oncology Society to open in 2004/2005.

References


