Pancreatoblastoma[1]

Author: Doctor Bernadette Brennan[2]
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[1]Adapted 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/

[2]Royal Manchester Children's Hospital, Hospital Road, M27 4HA Manchester, United Kingdom. bernadette.brennan@cmmc.nhs.uk

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 pancreatoblastoma 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 pancreatoblastoma 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.

-Gastronoma: severe gastrointestinal ulceration and diarrhea.

-VIPoma: watery diarrhea, hyperkalemic and achlorhydia.

-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 pancreatoblastomas. In order of frequency these were pancreatoblastoma, 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

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

Clinical description

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 hemorrhaging. Poor nutritional intake and the resultant weight loss may also be found.

Histopathology

Histologically, pancreatoblastoma exhibits dense cellularity with acinar differentiation and characteristic "squamoid corpuscules". 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

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage II	T3	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4	Any N	M0
Stage IVB	Any T	Any N	M1

Treatment

Surgery
Initial management requires an open biopsy and/or where feasible complete surgical resection.
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.
i) Infiltration of the porta hepatis including one or more of the following: portal vein and hepatic artery.
ii) Involvement of surrounding major vessels such as the aorta, inferior vena cava or celiac axis
iii) Metastatic disease

Chemotherapy
If the tumor is unresectable, then in view of the many similarities between pancreablastoma and hepatoblastoma, it is recommended that pancreatoblastoma is treated in accordance with SIOPEL 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.

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 SIOPEL PBL under the auspices of SIOPEL International Paediatric Oncology Society to open in 2004/2005.

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