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Original Research

Pancreatoblastoma in children: Clinical management and literature review

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ABSTRACT

Purpose: The aim of this study is to analyze the clinical and pathological features of pancreatoblastoma (PB) and to obtain better management for patients with relapsed or metastatic disease.
Methods: Four cases treated in our institution and 59 cases reported previously in the literature from the PubMed biomedical database (2000–2020) were reviewed and analyzed.
Results: Four cases with PB presented with abdominal pain and palpable abdominal masses, with the tumor size ranging from 5.2 to 18 cm in diameter. The invasion of the splenic vein and superior mesenteric artery, duodenum, and lymph nodes were risk factors for PB. Three cases were treated with combination therapy and showed favorable outcomes, while one case was treated with chemotherapy alone due to tumor progression and died of the disease. Squamous corpuscles were revealed in the tumor samples and considered a defining component for histological diagnosis.
Conclusions: Multidisciplinary diagnosis plays an important role in clinical management. The risk factors should be considered in the therapeutic stratification of PB before surgery.

Introduction

Pancreatoblastoma (PB) is an extremely rare pancreatic tumor that commonly occurs in infants and young children [1–3]. It comprises less than 1% of pancreatic tumors. The clinical presentations of PB are diverse and nonspecific, which leads to difficulties in its differentiation from other retroperitoneal tumors. Biological aggressiveness and elevated levels of serum α-fetoprotein (AFP) show similarities to hepatoblastoma [4]. The imaging features of CT and MRI are helpful in its differentiation from solid pseudopapillary neoplasms of the pancreas [5]. As such, a diagnosis of PB relies on its distinctive histological features [6].

PB is commonly considered to follow an indolent course and achieves long-term survival with surgical resection alone [7,8]; however, some studies have reported that the prognosis is poor in cases of metastasis or incomplete resection [9–11]. The standardized management for risk stratification in PB patients is rarely reported [9,12].

Moreover, there is limited data on the standard clinical treatment of relapsed and/or metastatic PB.

In this study, we describe the clinical characteristics, imaging features, serum parameters, pathological diagnosis, and treatment of four cases, as well as discuss the relevant literature, aiming to achieve better clinical management for patients with PB.

Materials and methods

Patients

In this study, four patients with PB hospitalized in our hospital between 2016 and 2020 were enrolled. Clinical data, including age at diagnosis, clinical presentation, site of disease, tumor size, serum AFP level, treatment modalities, and outcomes, were reviewed. The assessments of tumor location, size, extent of the tumor, and distant metastasis were analyzed by ultrasonography (US), computed tomography (CT), or positron emission tomography and computed tomography (PET-CT) (case 1). The treatment regimen of PLADO (cisplatin at 80 mg/m^2 on day

PB, pancreatoblastoma; AFP, serum α-fetoprotein; US, ultrasonography; CT, computed tomography; PET-CT, positron emission tomography and computed tomography; BWS, Beckwith-Wiedemann syndrome.

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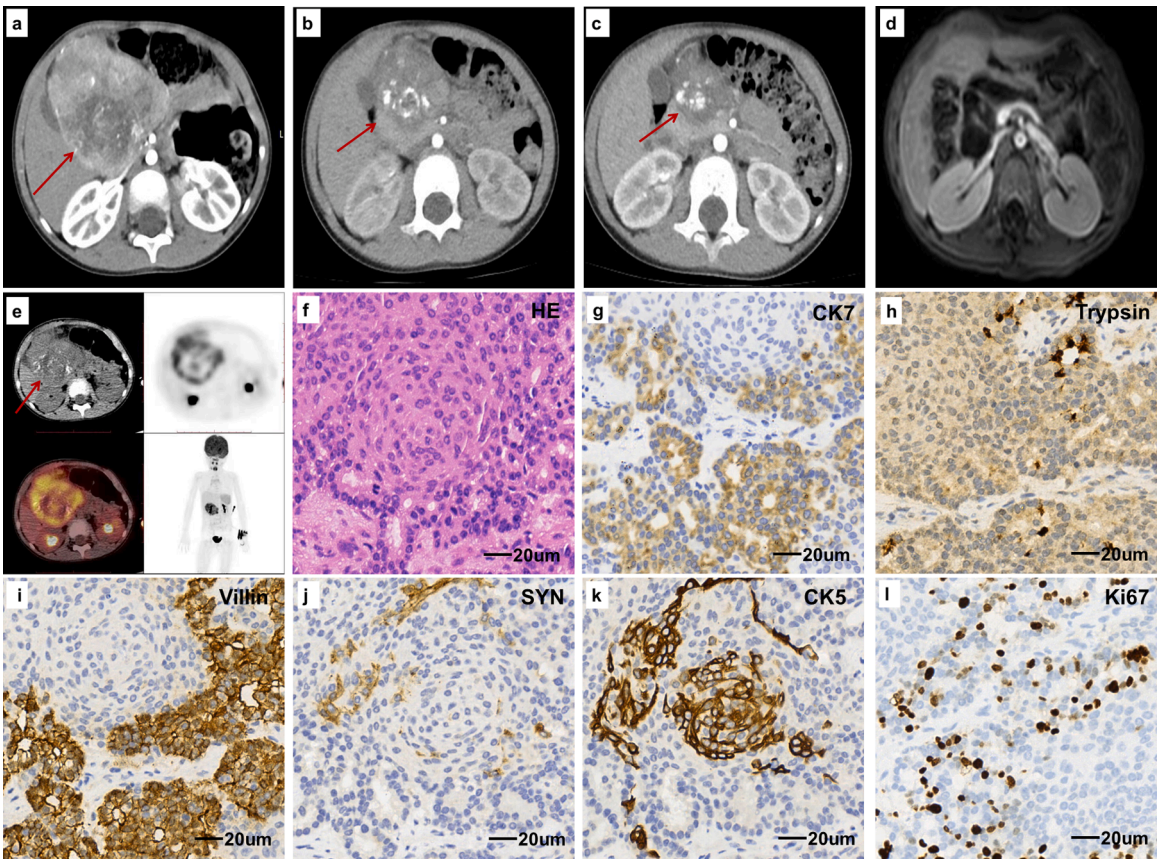

Fig. 1. Imaging, histopathological and immunohistochemical characteristics of PB in Case 1. (a) CT revealed a 7.6 × 7.5 cm mass in the pancreatic head with flocculent calcification and clear rim. (b) After the third cycle of chemotherapy, CT revealed a 5.5 × 4.7 cm hypoechoic mass, which was characterized as irregular, clear rim, and punctate hyperechoic. (c) CT showed that the tumor size was reduced to 3.5 × 3.1 cm after the fourth cycle. (d) There was no residual tumor or recurrence on postoperative CT. (e) PET-CT showed that the surrounding duodenum liver, gallbladder, and gastric wall were compressed by the tumor, and tumor biopsy was performed though laparoscopic surgery according to multidisciplinary suggestions. (f) The neoplastic cells presented an organoid arrangement of acinar, solid, or trabecular formations. Squamous corpuscles are shown (hematoxylin and eosin, original magnification × 400). Immunohistochemical staining of tumor cells showing positive expression of CK7 (g), trypsin (h), villin (i), and local positive expression of SYN (j). Squamous corpuscles showed positive expression of CK5 (k). Ki67 revealed the proliferation index of the tumor (l).

1; doxorubicin at 30 mg/m^2 on day 2,3) and ICE (ifosfamide at 1.5 g/m^2 on day 1–5, carboplatin at 450 mg/m^2 on day 1; etoposide at 100 mg/m^2 on day 1–3) were used. The literature search was conducted with the PubMed biomedical database, using keywords “pancreatoblastoma” and “pancreatoblastoma in children”. Additional studies derived from the references were also analyzed.

Results

Clinical features

There were three girls and one boy aged 3.6, 8.9, 5.5, and 4 years. Two patients presented with abdominal pain, and two patients presented with palpable abdominal masses. The imaging findings indicated well-defined heterogeneous masses in the pancreas, with tumor sizes of 7.6 cm, 5.2 cm, 18 cm, and 9.3 cm in maximum diameter, respectively. The invasion of the splenic vein and superior mesenteric artery, duodenum, and lymph nodes was observed. Liver recurrence was manifested in case 3. Cases 1 and 2 were treated with combination therapy (preoperative chemotherapy, pancreaticoduodenectomy, and postoperative chemotherapy), with a good outcome at follow-up. Case 3 underwent liver lobe resection and showed good outcome. Case 4 showed invasion of the splenic vein and superior mesenteric artery and died of severe ascites and multiple metastases.

Pathological features

Morphological features

Neoplastic cells usually showed an organoid arrangement of acinar, solid, trabecular, or ductal formations akin to acinar cell carcinomas. The solid component was comprised of polygonal tumor cells with whorled or nests, which were defined as squamous corpuscles. The nuclei were larger and more oval-shaped than those of the surrounding cells. The squamous corpuscles were detected in all tumors.

Immunohistochemical staining

Immunohistochemical staining showed evidence of acinar, endocrine, and ductal differentiation, according to trypsin, cytokeratin AE1/AE3, CK19, CK7, CK8, villin, and α1-AT staining. Endocrine markers, such as SYN and CgA, were focal positive. The squamous corpuscles were positive for CK5, but negative for CK7. Ki-67 ranged from 30 to 80%.

Case presentation

Case 1

A 3-year and 6-month-old girl was hospitalized in our unit due to an abdominal mass for 2 weeks. No tumor family history was provided. The physical examination showed a palpable abdominal mass below the right costal margin line. The AFP level reached to 2329.0 ng/ml

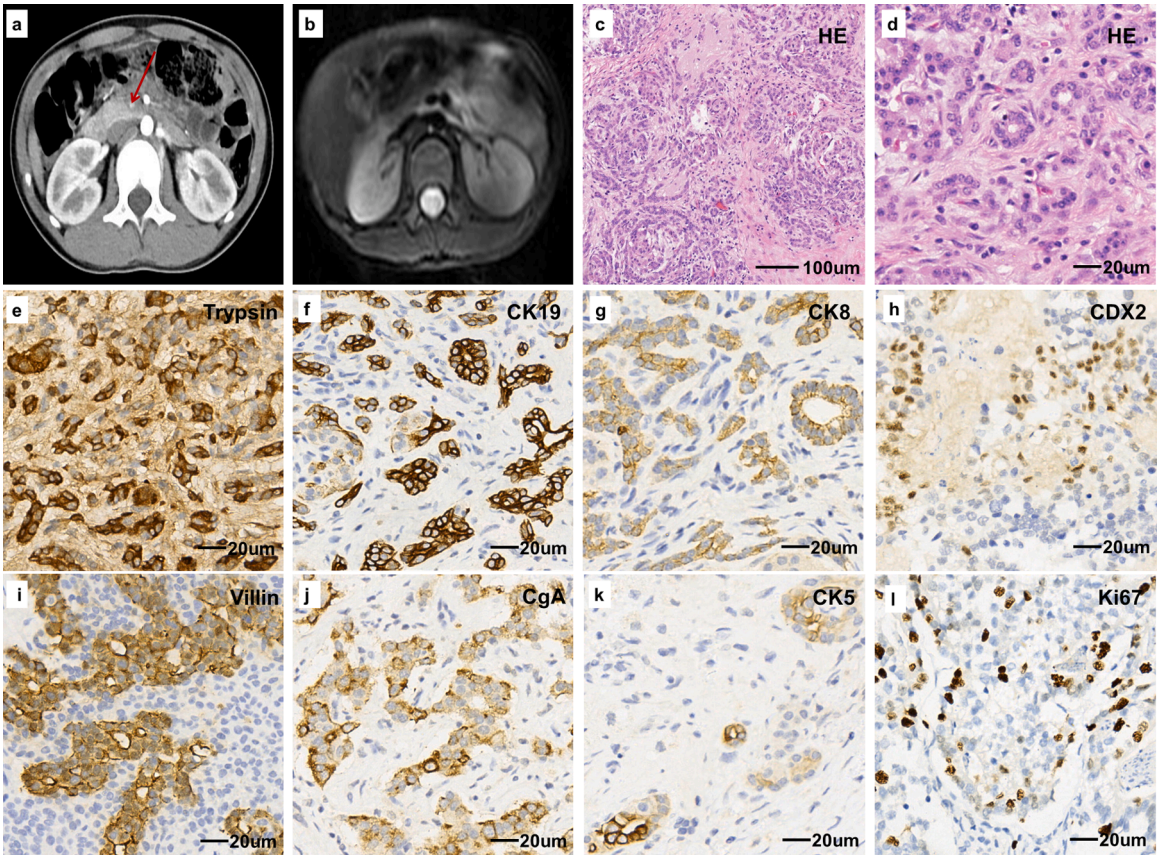

Fig. 2. Imaging, as well as histopathological and immunohistochemical characteristics of PB in Case 2. (a) CT revealed a soft tissue shadow below the head of the pancreas with a size of 5.2 × 5.2 cm and surrounding lymphatic enlargement. (b) No residual tumor on postoperative CT was observed. (c, d) The neoplastic cells presented acinar or trabecular formations (hematoxylin and eosin, original magnification × 100 and × 400). Immunohistochemical staining of tumor cells showing positive expression of trypsin (e), CK19 (f), CK8 (g), CDX2 (h), villin (i), and local positive expression of CgA (j). A few tumor cells showed squamous differentiation and expression of CK5 (k). Ki67 revealed the proliferation index of the tumor (l).

(normal, <20.0 ng/ml), and the AFP variant was 278.48 ng/ml (normal, 0–1 ng/ml). Increased serum LDH (508 U/L; normal range, 106–211 U/L) and NSE (69.8 ng/ml; normal range, 0–16.3 ng/ml) levels were presented. TORCH antigens, caused by *Toxoplasma gondii*, other (hepatitis viruses, parvovirus, human immunodeficiency virus, Epstein-Barr virus, syphilis), Rubella virus, Cytomegalovirus, and Herpes Simplex Virus were negative. US revealed a well-defined abdominal mass with heterogeneous echo in a local hospital. CT revealed a 7.6 × 7.5 cm mass in the pancreatic head with heterogeneous components, which was characterized by flocculent calcification and clear rim. The rich vasculum was identified by a CTA scan (Fig. 1a). The PET-CT image (Fig. 1e) showed that the surrounding duodenum liver, gallbladder, and gastric wall were compressed by the tumor, and tumor biopsy was performed though laparoscopic surgery according to multidisciplinary suggestions.

He was diagnosed with PB as pathological evidence. The patient was referred to oncologists and treated with four cycles of the PLADO regimen, consisting of cisplatin at 80 mg/m^2 on day 1 and doxorubicin at 30 mg/m^2 on day 2,3. CT revealed 5.5 × 4.7 cm (Fig. 1b) and 3.5 × 3.1 cm (Fig. 1c) masses, which were characterized by heterogeneous components and flocculent calcification after the second and fourth cycle of chemotherapy. The serum AFP level decreased to 159.0 ng/ml, 10.4 ng/ml, 3.49 ng/ml, and 4.02 ng/ml after the first, second, third, and fourth cycle, respectively. Similarly, the AFP variant level was <0.6 ng/ml after the third cycle. Subsequently, pancreaticoduodenectomy with Roux-en-Y end-to-end cholangiojejunostomy was performed. After surgery, the patient was treated with three cycles of the PLADO regimen. The follow-up data showed a good outcome for 11 months. There was no residual tumor or recurrence on postoperative US and CT (Fig. 1d). The serum AFP level was <5 ng/ml, and the AFP variant was <0.6 ng/ml.

Case 2

An 8-year and 9-month-old girl was admitted to a local hospital with intermittent nausea for 2 months. A palpable abdominal mass was identified by her parents 1 month prior to hospitalization. No family members presented with tumors. The physical examination showed an abdominal mass without enlarged lymph nodes. US showed a heterogenous echo in the middle of the abdomen and para-aortic hypoecho nodules. CT revealed a soft tissue shadow below the head of the pancreas with a size of 5.2 × 5.2 cm and surrounding lymphatic enlargement. Moreover, the duodenum and superior mesenteric vein invasion were noted.

Laboratory tests showed an elevated AFP level (323.00 ng/ml). Serum LDH (220 U/L; normal range, 106–211 U/L) and NSE (21.2 ng/ml; normal range, 0–16.3 ng/ml) levels were slightly elevated. With these findings, a biopsy of the pancreatic head tumor was performed though laparoscopic surgery. The patient was diagnosed with PB according to the pathology results.

For further treatment, the patient came to our institution. Chemotherapy was given (cisplatin at 80 mg/m^2 on day 1; doxorubicin at 30 mg/m^2 on day 2,3). After the first cycle of chemotherapy, the tumor size was reduced to 4.1 × 3.5 cm (Fig. 2a), and the serum AFP level was reduced to 20 ng/ml. After the second cycle of chemotherapy, the serum AFP level was reduced to 6.83 ng/ml, and the AFP variant was <0.6 ng/ml.

Subsequently, pancreatoduodenectomy was performed. Four cycles of the aforementioned chemotherapy regimen was given after surgery.

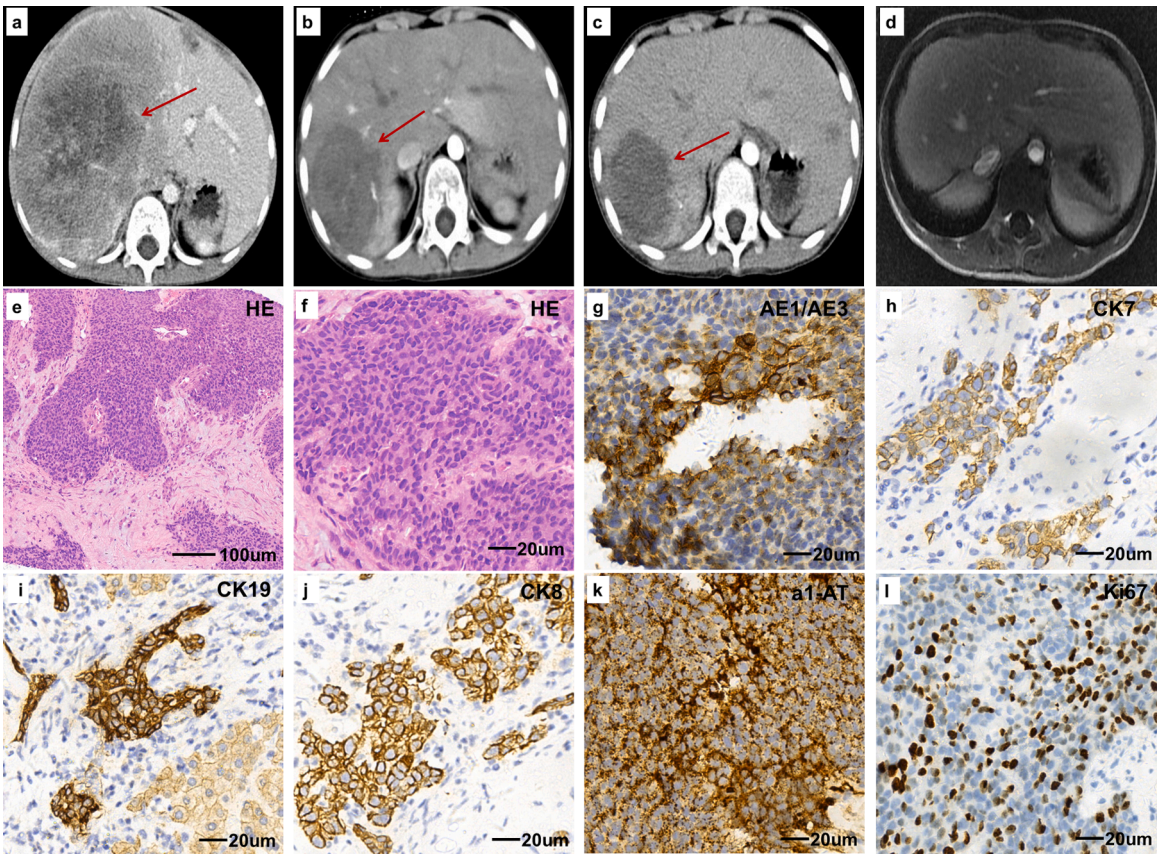

Fig. 3. Imaging, histopathological and immunohistochemical characteristics of relapsed PB in Case 3. (a) Enhanced CT revealed a huge mass in the liver. (b) After the second cycle of chemotherapy, CT revealed the tumor size was 6.8 × 5.3 cm. (c) CT showed that the tumor size was 5.6 × 4.6 cm after the fourth cycle. (d) There was no residual tumor on postoperative CT. (e, f) The neoplastic cells presented as solid, flake, or nested formations (hematoxylin and eosin, original magnification × 100 and × 400). Immunohistochemical staining of tumor cells showing positive expression of AE1/AE3 (g), CK7 (h), CK19 (i), CK8 (j), and a1-AT (k). Ki67 revealed the proliferation index of the tumor (l).

The follow-up data showed that there were no signs of recurrence for 9 months (Fig. 2b). The serum AFP level was 0.91 ng/ml, and the AFP variant was <0.6 ng/ml.

Case 3

A 5-year- and 5-month-old boy who suffered with abdominal pain for 1 month was hospitalized in a local hospital. An abdominal mass was detected by a physical examination. The serum AFP level was 1064.31 ng/ml, and a huge mass was identified in the body and tail of the pancreas by US. Enhanced CT revealed a huge mass with a size of 18 × 10 × 10 cm, and the duodenum was compressed by the tumor. A resection of the pancreatic tumor was performed, and PB was diagnosed based on morphological and immunohistochemical features. His family refused further postoperative chemotherapy because of socio-economic reasons.

After 10 months, he developed liver metastasis and was transferred to our unit. US showed liver mass with a size of 14.9 × 13.5 cm. CT showed multiple intrahepatic nodules and enlarged portal/hilar lymph nodes with abundant blood vessels. The serum AFP level increased to 121,000.00 ng/ml. Four cycles of the PLADO regimen were administrated. The serum AFP level was reduced to 7069.00 ng/ml and then 519.70 ng/ml, and the tumor size was 10.7 × 7.1 cm (US) and then 6.8 × 5.3 cm (CT) (Fig. 3b) after the first and second cycle, respectively. After the fourth cycle of chemotherapy, the AFP value was 36.85 ng/ml, and the tumor size was 5.6 × 4.6 cm by CT (Fig. 3c). The patient underwent resection of segments 6 and 7 of the right liver lobe. The serum AFP level decreased to 5.61 ng/ml on the first day after the surgery. Postoperative chemotherapy with cisplatin and doxorubicin was given for four cycles. Subsequently, the serum AFP level was 3.7 ng/ml. CT showed multiple small abnormal signals in the liver, further treatment was given according to the ICE regimen as follows: ifosfamide at 1.5 g/m^2 on day 1–5, carboplatin at 450 mg/m^2 on day 1, and etoposide at 100 mg/m^2 on day 1–3. The follow-up data showed that there were no signs of recurrence for 43 months (Fig. 3d).

Case 4

A 4-year-old girl suffering from abdominal pain for 3 months was admitted to a local hospital. The physical examination showed moderate jaundice of the skin mucosa. CT showed a 9.3 × 8.8 cm heterogeneous mass with nodular calcification at the right retroperitoneal region. The adjacent organs, including the liver and gallbladder, were compressed. Multiple tumor thrombi in the splenic vein and superior mesenteric artery were detected. The laboratory examination showed an elevated serum AFP level (50.53 ng/ml). US-guided tumor biopsy was performed. According to the pathology results, she was diagnosed with PB.

She was transferred to our unit and was treated with the PLADO regimen. After one cycle, the patient's jaundice subsided, and the serum AFP value was reduced to 23.87 ng/ml. After three cycles, the serum AFP level was reduced to 11.0 ng/ml, and the tumor size was 4.2 × 5.1 cm by CT. Tumor thrombi in the splenic vein and superior mesenteric artery were still present. Unfortunately, her family refused subsequent treatment for socio-economic reasons. After 15 months, she died of progressive disease and multiple organ failure.

Table 1
Pancreatoblastoma in children and the literature review.

No.	Age	Gender	Signs and Symptoms	Location	Size (cm)	AFP (ng/ml)	Pathology	Metastases/ invasion	Type of surgery	Chemotherapy/radiotherapy Preoperative	Postoperative	Outcome (months)	Refs.
1	Prenatal (GA: 20wk)	F	Abdominal mass BWS	H	11.0	>220.0↑	Squamous corpuscle	N	Complete resection	N	N	Excellent (24)	[29]
2	Prenatal (GA: 28wk)	M	Abdominal mass BWS	B-T	4.0	U	Focal squamous	N	Complete resection	N	N	Excellent (26)	[15]
3	Prenatal (GA: 30wk)	M	Abdominal mass	B-T	4.2	52876.0↑	Squamous corpuscle	N	Distal pancreatectomy	N	N	Excellent (10)	[14]
4	Prenatal (GA: 33wk)	F	Abdominal distension BWS	T	14.1	3,018,290↑	U	N	partial excision	Yes		Excellent (18)	[30]
5	Prenatal (GA: 34wk)	F	Abdominal mass	T	4.0	ND	Cords and tubules	N	Complete resection	N		Excellent (15)	[31]
6	0 y	M	BWS	B	4.0	Normal	Focal squamous	N	Complete resection	N	N	Excellent (26)	[9]
7	3 d	M	Jaundice	B-T	7.5	>1000↑	ND	N	Complete resection	N	N	Excellent	[1]
8	2 mo	M	BWS	B	4.3	23,748↑	Acinar and trabecular Squamous nests	N	Pancreaticojejunostomy	N		Excellent (40)	[6]
9	2 mo	M	BWS	H	4.5	4639↑	Glandular and solid patterns	N	Complete resection	N		Excellent (60)	[18]
10	3 mo	M	Abdominal mass	Mesocolon	10.0	> 1000 ↑	Squamous corpuscle Hemorrhage, necrosis	N	Complete resection	N (refuse)		Excellent (24)	[17]
11	3 mo	F	Abdominal mass	T	ND	ND	Acinar and trabecular Squamous nests	N	Complete resection	N		Excellent (39)	[8]
12	6 mo	F	Diarrhea	H-B-T	7.7	54,000↑	Acinar, trabecular Squamous corpuscles	Lung Liver		2 CDDP+VP16		Died	[6]
13	7 mo	M	Abdominal mass	T	6.9	57.55	Acinar, trabecular Squamous corpuscles	N	Spleen-preserving distal pancreatectomy	N	N	Excellent (52)	[6]
14	1 y	M	Subcutaneous mass	H	2.0	Normal	U	Cutis Mediastinum	Biopsy of subcutaneous nodule	cyclophosphamide, doxorubicin, vincristine, ifosfamide, vinblastine; Radiotherapy		Toxic death	[9]
15	1 y	M	Abdominal mass	T	8.5	66	Acinar, trabecular Squamous nests	N	Distal pancreatectomy with en bloc splenectomy	N	N	Excellent (50)	[6]
16	2 y	F	Abdominal pain, abdominal Mass	H	7.0	564.85 ↑	Acinar, trabecular Squamous nests	N	Central pancreatectomy with Roux-en-Y end-to end pancreaticojejunostomy	N	N	Excellent (74)	[6]
17	2 y	M	Abdominal Mass	H	ND	450↑	Acinar and trabecular areas Squamous nests	Liver	Complete Cephalopancreatoduodenectomy	2 carboplatin-doxorubicin		Excellent (5)	[8]
18	2 y	M	Abdominal distention Vomiting Failure-to-thrive	B-T	11.5	ND	Solid islands Abortive ducts Squamous corpuscle	Liver	Complete resection	2 CDDP cyclophosphamide, adriamycin, cisplatin, and etoposide; Cyclophosphamide Dacarbazine	Autologous peripheral blood stem cell transplantation	Recurrence, excellent (120)	[24]
19	3 y	M	Abdominal mass	H-B	U	48.0	ND		Pancreatoduodenectomy		Pirarubicin Carboplatin	Excellent (72)	[21]

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Table 1 (*continued*)

No.	Age	Gender	Signs and Symptoms	Location	Size (cm)	AFP (ng/ml)	Pathology	Metastases/ invasion	Type of surgery	Chemotherapy/radiotherapy Preoperative	Chemotherapy/radiotherapy Postoperative	Outcome (months)	Refs.
								Lung lymph nodes Portal veins		Cyclophosphamide Pirarubicin cisplatin	Etoposide Melphalan PBSCT		
20	3 y	F	Abdominal mass	B	8.6	2140 ↑	Acinar, trabecular Squamous nests	N	Central pancreatectomy with Roux-en-Y end-toend pancreaticojejunostomy	2 VAC 2 VCE		Excellent (50)	[6]
21	3 y	M	Abdominal mass	B-T	9.8	6412↑	Acinar, trabecular Squamous corpuscles	N	Central pancreatectomy with Roux-en-Y end-toend pancreaticojejunostomy	N		Excellent	[6]
22	3 y	F	Abdominal pain	H-B-T	15.3	ND	Acinar, trabecular Squamous corpuscles	Tumor thrombus in splenic vein	N	2 CDV 2 OPEC		Died of disease	[6]
23	3.6 y	F	Abdominal mass	H	7.6	2329.0 ↑	Acinar Squamous corpuscles	Duodenum	Pancreaticoduodenectomy with Roux-en-Y end-toend cholangiojejunostomy	PLADO	PLADO	Excellent (11)	Current Report (case 1)
24	4 y	F	Abdominal Pain	H	6.0	394.6 ↑	Solid, acinar, glandular, and undifferentiated structures, necrosis and nests of squamous cells	Lymph nodes	Complete resection	NO		Excellent (7)	[2]
25	4 y	F	Abdominal Pain	U	9.3	50.53	Small round cell Necrosis	Splenic vein and superior mesenteric artery	No	PLADO		Died of severe ascites and multiple metastases	Current Report (case 4)
26	4 y	M	Abdominal pain Jaundice	B	8.0	↑	U	Distant lymph nodes	Complete resection	PLADO +etoposide VAC-ICE Melphalan Radiotherapy	N	Excellent (24)	[9]
27	4 y	F	Abdominal pain	B	9.0	Normal	Squamous corpuscles Acinar, glandular and undifferentiated structures	Superior mesenteric artery	Complete resection	PLADO Ifosfamide Etoposide		Excellent (84)	[19]
28	4 y	M	Abdominal pain	B-T	10.5	1578 ↑	U	Colon Liver	Distal pancreatectomy, splenectomy, and segmental colectomy	PLADO	liver metastases, Vinorelbine Cyclophosphamide	No chemotherapy given after surgery. Died	[11]
29	4 y	M	Abdominal mass	B-T	10.4	3616↑	Acinar, trabecular Squamous corpuscles	Splenic vein, Mesenteric vein	Pylorus-preserving pancreaticoduodenectomy	6 PLADO		Excellent (39)	[6]
30	4 y	F	Abdominal pain jaundice	H	4.5	60	Acinar, trabecular Squamous corpuscles	N	Pylorus-preserving pancreaticoduodenectomy	1 CDV+5-FU 1 OPEC	D	Excellent (23)	[6]
31	4 y	M	Abdominal pain	H	4.8	2.08	Acinar, trabecular Squamous corpuscles	Liver, Mesenteric vein	Abdominal cavity drainage	3 AVCP 2 IEV 1 IFO+VP+VCR		Died of severe ascites and multiple metastases	[6]
32	4 y	M	Abdominal pain	H	4.0	ND	Acinar, trabecular Squamous corpuscles	N	Pancreaticoduodenectomy (Whipple operation)	4 OPEC		Excellent (42)	[6]
33	4 y	M	Abdominal pain	T	9.1	426.87↑	Acinar, trabecular Squamous corpuscles	Liver Splenic vein	Spleen-preserving distal pancreatectomy resection of liver metastatic lesions	5 OPEC		Excellent (48)	[6]
34	4 y	F	Jaundice	H	9.7	7000↑	Acinar, trabecular Squamous corpuscles	Liver	Pancreaticoduodenectomy (Whipple operation)	4 CDV		Lost (6)	[6]
35	4 y	M	Abdominal pain	B	U	ND		Liver	Subtotal pancreatectomy, complete hepatectomy		Yes	Excellent (84)	[32]

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Table 1 (*continued*)

No.	Age	Gender	Signs and Symptoms	Location	Size (cm)	AFP (ng/ml)	Pathology	Metastases/ invasion	Type of surgery	Chemotherapy/radiotherapy Preoperative	Postoperative	Outcome (months)	Refs.
							Acinar Squamous corpuscles Necrosis			cisplatin, 5FU, vincristine, and doxorubicin			
36	4.6 y	F	Abdominal pain	H	4.4	394.60↑	Acinar pattern, and Squamous corpuscles	N	Pancreatoduodenectomy	N	N	Excellent	[1]
37	4.7 y	M	Diarrhea	Root of the mesentery	12.5	391.8↑	Acinar pattern, Squamous corpuscles	Mesenteric arteries	Tumorectomy	Isofosfamide Vindesine Carboplatin Adr, VP16	Isofosfamide Vindesine Carboplatin Radiotherapy	Excellent (6)	[1]
38	4.8 y	F	Abdominal mass Vomiting	H-B	10.0	9600↑	Squamous corpuscles Glandular	N	Complete resection	Cyclophosphamide Pirarubicin Etoposide Cisplatin	Cyclophosphamide Pirarubicin Etoposide Cisplatin	Excellent (60)	[33]
39	5 y	M	Abdominal pain	B-T	12.0	↑	U	N	Incomplete resection	Doxorubicin Vincristine Etoposide	Radiotherapy	Excellent (48)	[9]
40	5 y	F	Abdominal pain Abdominal mass Anorexia	B-T	9.8	2307.42↑	Acinar, trabecular Squamous corpuscles	Tumor thrombus in splenic vein	Distal pancreatectomy with elective splenectomy	2 CDV 2 OPEC		Excellent (81)	[6]
41	5 y	M	Abdominal pain Fever	B-T	10.6	68.87	Acinar, trabecular Squamous corpuscles	Splenic vein	Spleen-preserving distal pancreatectomy+splenic vein resection	2 CDV 2 OPEC		Excellent (48)	[6]
42	5 y	M	Abdominal pain	B	11	55117↑	Squamous corpuscles Acinar, epithelial acinar cells	Liver, splenic vein and transverse colon	Completer resection	No	cisplatin 80 mg/m2, 24 h constant infusion; carboplatin 500 mg/m2, 1 h infusion and doxorubicin	Died (14)	[10]
43	5.5 y	M	Abdominal Pain	B-T	U	1064.31 ↑	Squamous corpuscles Necrosis	Liver	Pancreatic tumor resection and segments 6 and 7 of the right liver lobe resection	PALDO	PALDO ICE	Recurrence and Excellent (96)	Current Report (case 3)
44	6 y	F	Abdominal pain Abdominal mass Anorexia	H	7.5	1280↑	Acinar and trabecular	Lymph nodes Liver	Complete resection	PVB Cyclophosphamide Dactinomycin		Died (36)	[8]
45	6 y	F	Abdominal pain Fever Vomiting	H-B	9.0	884.8↑	Squamous corpuscle	N	pylorus-preserving pancreatoduodenectomy	cyclophosphamide, etoposide, vincristine, pirarubicin and cisplatin radiation and stem cell transplantation SCT	Irinotecan and vincristine	Excellent (4)	[23]
46	6 y	M	Abdominal mass	H-B	15.4	1662↑	Acinar, trabecular Squamous corpuscles	N	Spleen-preserving distal pancreatectomy	N		Excellent (11)	[6]
47	6 y	M	Abdominal distension	H	10.0	ND	Acinar, trabecular Squamous corpuscles	Liver	Pancreaticoduodenectomy (Whipple operation)	N		Lost (12)	[6]
48	7 y	M	Abdominal pain Abdominal mass	H-B-T	12.5	209.19↑	Acinar, trabecular Squamous corpuscles	Splenic vein, Mesenteric vein Portal vein	Distal pancreatectomy with elective splenectomy	CDV OPEC CDV+5-FU IFO+P+VP-16		Lost (12)	[6]
49	7 y	F	Abdominal mass	B	10.5	Normal	Squamous corpuscles Acinar and tubular structures	N	Complete resection	N	Cisplatin, doxorubicin A course: cisplatin, vincristine;	Excellent (90)	[19]

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Table 1 (*continued*)

No.	Age	Gender	Signs and Symptoms	Location	Size (cm)	AFP (ng/ml)	Pathology	Metastases/ invasion	Type of surgery	Chemotherapy/radiotherapy Preoperative	Postoperative	Outcome (months)	Refs.
											B course: ifosfamide etoposide		
50	7 y	F	Abdominal pain Abdominal distension	T	U	2275↑	U	Mesenteric root, portal vein, liver	A distal pancreatectomy with splenectomy and liver transplantation	PLADO	No	Excellent	[26]
51	8 y	M	Abdominal mass	B-T	13.2	6069↑	Acinar, trabecular Squamous corpuscles	Tumor thrombus in Kidney vein Splenic vein	Spleen-preserving distal pancreatectomy and kidney vein and splenic vein resection with restruction of kidney vein	CDV OPEC		Lost (1)	[6]
52	8 y	M	Vomiting Abdominal mass Abdominal pain	T	21.0	> 2100.0	Organized structures Squamous corpuscles Acinar structure	N	Complete excision and splenectomy	N	N (refuse)	Excellent	[7]
53	8 y	F	Abdominal mass	T	15.0	> 1800.0	Organoid structures Squamous corpuscles Acinar structure	N	Complete excision	N	N (refuse)	Excellent	[7]
54	8 y	F	Abdominal mass	B-T	U	1940↑	Acinar and trabecular Squamous corpuscles	Liver, portal vein thrombus	Incomplete resection	PVB Cyclophosphamide Dactinomycin	Radiotherapy	Died (30)	[8]
55	8.9 y	F	Abdominal mass	H	4.1	323↑	Squamous corpuscles Acinar	Lymph nodes, duodenum	Pancreaticoduodenectomy	PLADO	PLADO	Excellent	Current Report (case 2)
56	9 y	F	Abdominal mass	T	10.0	> 1500↑	Organoid structures Squamous corpuscles Acinar structure	N	Complete excision	N	N (refuse)	Excellent	[7]
57	9 y	F	Abdominal mass	B	ND	1400↑	Acinar and trabecular Squamous corpuscles	Lymph nodes	Complete excision	2IVA 4 CDDP-doxorubicin	No	Excellent (60)	[8]
58	10 y	M	Abdominal pain Jaundice	H	ND	ND	Acinar, trabecular Squamous corpuscles	N	Pancreaticoduodenectomy (Whipple operation)	2 CDDP+ ADR/VP16		Excellent (156)	[6]
59	11 y	M	Abdominal mass	H	U	20	Acinar and trabecular Squamous corpuscles	Lymph nodes	No possible resection	CDDP-doxorubicin	Radiotherapy	Liver metastases, Died (9)	[8]
60	11 y	F	Abdominal pain	U	U	241.4 ↑	U	Liver, lymph nodes	Pylorus-sparing pancreaticoduodenectomy (Whipple)	gemcitabine and cisplatin	doxorubicin, cisplatin and carboplatin	Died of progressive disease	[11]
61	12 y	M	Abdominal pain Anorexia Weight loss	B-T	5.9	524 ↑	Solid and tubular	Liver	Resection of tumor and intrahepatic masses	CDDP Vincristine FU Gemcitabine		Excellent (72)	[34]
62	14 y	F	Nausea Vomiting Abdominal pain	B-T	13.5	N	U	Peritumoral fibrosis and splenic vessels	Complete excision	PLADO Carboplatin Etoposide	Autologous hematopoietic stem cell transplantation	Excellent (48)	[25]
63	18 y	M	Abdominal pain Abdominal mass Jaundice	B-T	10.0	U	Acinar and glandular Squamous corpuscles	Liver	Complete excision	Adriamycin Gemcitabine Radiotherapy		Progressive disease of hepatic masses, invading the pancreatic head and enlarged tracheobronchial lymph nodes. Died (26)	[35]

IVA, Ifosfamide+Vincristine+Dactinomycin; PVB, Cisplatin+Vinblastine+Bleomycin; PLADO, Cisplatin+Doxorubicin; IE, Ifosfamide+Etoposide; CDV, Cyclophosphamide+Daunorubicin+Vincristine; OPEC, Vincristine+Cyclophosphamide+Cisplatin+Etoposide; H, Head; B, Body; T, Tail; U, Unknown; N: None; VP16: Etoposide.

Discussion

PB is rare in children, typically affecting children between 1 and 8 years of age [13]. Due to the lack of comprehensive and effective diagnoses and treatment strategies, we reviewed 63 cases with PB, including our four cases and 59 cases reported previously in the literature [1,2,6–11,14,15,17–19,21,23–26,29–35] (Table 1). There were 35 males and 28 females. The age distribution of the 63 cases showed that more than 90% of patients were diagnosed before age of 10 years (Supplementary Fig. 1). Most patients presented with symptoms, including abdominal masses (30 /63, 47.6%) and abdominal pain (28/63, 44.4%). Obstructive jaundice occurred in 7.9% of patients (5/63). Digestive system manifestations, including abdominal distension, diarrhea, and vomiting, were noted in some children (8/63, 12.7%). Anorexia (3/63, 4.8%), fever (2/63, 3.2%), and failure to thrive (1/63, 1.6%) were less common. Beckwith–Wiedemann syndrome (BWS) is an overgrowth syndrome characterized by macrosomia, macroglossia, abdominal wall defects, organomegaly, hemihypertrophy, ear anomalies, renal abnormalities, and neonatal hypoglycemia [14–16]. In our reviewed cases, 6/63 (9.5%) presented with BWS [6,9,15,18,29 [30]]. Due to the rarity of PB complicated by BWS, the clinical treatment was still undefined.

Imaging findings suggested that tumors were more commonly located in the body-tail, head-body-tail, and head-body (23/63, 30%), followed by the head (17/63, 27.0%), tail (10/63, 15.9%), and body (9/63, 14.3%) of the pancreas. Weksberg et al. reported that tumors adhering to the transverse mesocolon may originate from ectopic pancreatic tissue in the mesentery [17]. Large-size tumors with ill-defined borders, calcification, absence of hemorrhage, intertumoral vessels, and peripancreatic vessel invasion are the common features.

A definitive diagnosis of PB relies on the histological identification of epithelial differentiation (acinar, glandular, and trabecular architectures) and squamous corpuscles. The squamous corpuscles are unique, and they distinguish PB from neuroblastoma, hepatoblastoma, and other small round cell tumors [1,10,14,18]. In the immunohistochemical investigation, tumors were positive for trypsin, cytokeratin AE1/AE3, CK19, CK7, CEA, and VIM. The areas of squamous differentiation were also marked by CK5 and EMA. Endocrine markers, including SYN, CgA, and CD56, were positive seldomly.

In the cases we reviewed, more than half of the patients had metastases or invasion of the surrounding tissues (35/63, 55.5%). The liver (16/35, 45.7%) and veins (16/35, 45.7%) are the most common site of metastasis, although metastasis may also occur in regional lymph nodes (7/35, 20.0%), duodenum and colon (4/35, 11.4%), and lung (2/35, 5.7%). Therefore, the risk factors should be considered in the therapeutic stratification of PB, including vein involvement, extrasplenic abdominal disease, distant metastases, lymph node metastases, tumor rupture, and intraperitoneal hemorrhage [6,8,19]. Moreover, we observed that 14 cases experienced recurrence or died of progressing disease. In this series, 71% (10/14) of the children were older than 3 years old, suggesting that age might be considered in the therapeutic stratification of PB.

According to the risk factors, PB can be further divided into low-, intermediate-, or high-grade by the multi-disciplinary team at initial diagnosis. Complete surgical resection is strongly recommended, if achievable. The first-line of treatment is based on complete tumor resection, followed by chemotherapy (cisplatin and doxorubicin), which presents favorable outcomes [11,20]. Preoperative chemotherapy is recommended to shrink the tumor and to achieve the possibility of complete resection in intermediate- or high-grade PB [1,2,6,7,19,20]. Despite the small numbers, patients with an intermediate-grade show a better response in preoperative chemotherapy of PLADO or ICE-based regimens (etoposide, ifosfamide, and carboplatin) [1,9,19,21,22].

Patients with distant metastases are identified as high-grade PB. Although there are no strict recommendations, radiotherapy is performed in PB patients if the tumors do not respond to chemotherapy, or if recurrent, residual, and metastatic disease is present [3,8,19,23]. Several studies have reported that autologous hematopoietic stem cell transplantation has meaningful efficacy in a few cases of tumor recurrence [21,23–25], suggesting it might be adopted in patients with high-grade PB. Picado et al. reported that liver transplantation may have a favorable outcome in pediatric PB with metastatic livers [26].

AFP is a glycoprotein that is derived from embryonic endoderm tissue cells. The serum AFP level is usually increased in PB, hepatoblastoma, and germ cell tumors, such as yolk sac tumors in children [27, 28]. In our study, patients mostly show elevated serum AFP levels (>100 ng/ml, 38/50, 76%). After complete resection of the tumors, the AFP level in all patients was reduced, returning to the normal range at follow-up. These findings indicate that serum AFP might serve as a valuable tumor marker for preoperative diagnosis, and it can even indicate therapeutic effect and postoperative recurrence in PB patients.

In conclusion, PB is considered a curable tumor, and thus, a multidisciplinary diagnosis should be made early. Squamoid nests are considered as a defining component of histological diagnosis. The risk factors should be considered in the therapeutic stratification of PB.

Supplementary

Fig. 1. Age and sex-specific incidence of 63 patients for PB. The first peak was observed before 1 year of age, and the second peak was observed at 4 years of age. The distribution of males and females showed no significant differences.

Ethics approval

This study was approved by the ethics committee of the Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine.

Informed consent

All patients enrolled provided written informed consent.

CRediT authorship contribution statement

Tingting Liu: Conceptualization, Visualization, Writing – original draft, Investigation, Formal analysis, Writing – review & editing. **Tong Zhao:** Conceptualization, Visualization, Writing – original draft, Investigation. **Cuicui Shi:** Conceptualization, Visualization, Writing – original draft. **Lei Chen:** Conceptualization, Visualization, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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