

Pancreatoblastoma in a Teenage Patient

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ZD originally presented in June 1996 at age 18 with abdominal pain attributed to a blow to the abdomen sustained while wrestling. It originated in the epigastrium and radiated to the back and left upper quadrant. A 10-lb weight loss and diarrhea had also been noted. The patient had no other significant medical history. There was no significant family history of cancer. The initial work up included an upper gastrointestinal series, which suggested mild duodenitis. An abdominal computed tomography (CT) scan showed a 9 × 4 × 8 cm necrotic mass in the head of the pancreas that enhanced with intravenous contrast and appeared to invade the superior mesenteric artery and vein. Fine-needle aspiration was read as consistent with pancreatoblastoma. CA-19-9 level was 4 U/mL. Serum alpha-fetoprotein (AFP) was not checked.

Since the tumor was deemed to be unresectable because of the appearance on CT scan, he underwent combination chemotherapy with continuous-infusion 5-fluorouracil (5-FU) and radiation therapy. The patient had a partial response to the treatment. He then underwent a radical resection consisting of partial pancreatectomy (Figure 1) and right hemicolectomy forced by ischemia of the right colon after pancreatic mass resection. Pathologic examination of the specimen revealed a completely resected 8 × 7 × 3.5 cm malignant epithelial and mesenchymal necrotic tumor consistent with pancreatoblastoma with 2 negative lymph nodes (Figures 2A and 2B).

The patient did well subsequently. However, approximately 3.5 years later he began to have right upper quadrant discomfort and pleuritic chest pain. Chest CT showed a 3.3 × 6.2 cm pleural-based mass in the right



Figure 1. Pancreatoblastoma resection in operating room.

lung, as well as multiple other nodules as large as 3.8 × 6.9 cm. There was no sign of recurrent abdominal disease. AFP level was 1156.7 ng/mL. CT-guided biopsy of the lung mass demonstrated a primitive “blastemal”-type epithelial and mesenchymal neoplasm consistent with metastatic pancreatoblastoma (Figures 3A and 3B). He was begun on chemotherapy with vinblastine 0.11 mg/kg days 1–2, ifosfamide 1200 mg/m² days 1–5, and cisplatin 20 mg/m² days 1–5 for 4 cycles. He had a good radiographic response and an excellent tumor marker response with the AFP level dropping to 27.9 ng/mL. He then underwent a right middle lobectomy, anterior segmentectomy right upper lobe, wedge resection of the right lower lobe, and resection of a diaphragmatic nodule. His AFP level dropped further to a low of 2.6 ng/mL.

Nine months later on a restaging CT scan he was found to have an increase in the size of a small left lung nodule and his AFP level had increased to 16.7 ng/mL.

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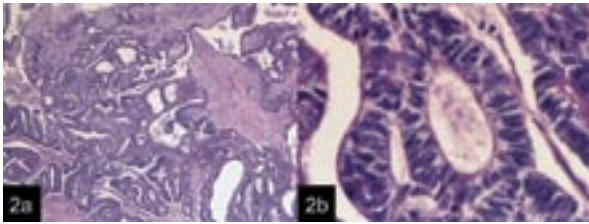


Figure 2. (A) Large irregular tubular structures are embedded in a dense fibrotic stroma. (B) Higher magnification highlighting the polarized columnar cells lining the glandular spaces.

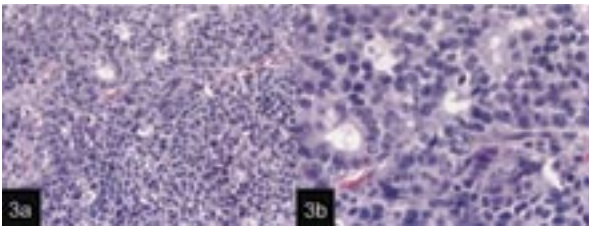


Figure 3. (A) Undifferentiated, "blastemal" component of the recurrent pancreatoblastoma. (B) Higher magnification demonstrating few acini bordered by immature cuboidal cells.

Abdominal CT showed no evidence of recurrent disease. He underwent wedge resection of this nodule. Since this last resection in June 2001, AFP level has been stable at 3.7–6.5 ng/mL and the patient remains without radiologic evidence of disease one and a half years posttreatment. He is clinically doing well and is followed with serial AFP measurements and CT scans. He is in college and without physical limitation.

Discussion

Pancreatoblastoma is a rare malignant tumor of the pancreas, comprising <1% of all pancreatic tumors.¹ Most cases have been observed in children with just over 60 cases reported in the literature.² Childhood cases of pancreatoblastoma occur primarily between the ages of 1–8 years, with a mean age of 4 years.^{3–5} Congenital examples have been reported. In adults, pancreatoblastoma is extremely rare.^{6,7} The age of adults with pancreatoblastoma ranges from 19 to 68 years,⁸ with an average age of approximately 40 years.⁵ The clinical course of pancreatoblastoma is more indolent in children than in adults, with reported adult median survival in one series of 18 months.⁵ Pancreatoblastoma appears to be more common in male patients and almost half of the reported cases have occurred in people of Asian descent. These tumors are typically slow-growing and may not cause symptoms. Any symptoms are usually from mass effect from the tumor.⁵ Approximately

half of all pancreatoblastomas arise in the head of the pancreas but rarely cause obstruction. The soft consistency of the tumor may account for the relative lack of local compression.³ The tumor invades local structures, and the most common site for metastases is the liver, seen in about a third of patients. Other sites of metastases are the bone, lymph nodes, and lung.⁵

The first reported case of pancreatoblastoma was described by Becker in 1957 in an infant.⁹ Frable and coworkers gave the first histopathologic description in 1971, labeling the tumor an "infantile-type" carcinoma of the pancreas.¹⁰ Kotoo and colleagues then renamed the tumor pancreatoblastoma in 1977 because of its resemblance to fetal pancreatic tissue of approximately 7 weeks' gestation.¹¹ Microscopically, pancreatoblastomas resemble incompletely differentiated acinar cells of the pancreas, with sheets and nests of polygonal cells with both solid and acinar growth patterns. Squamoid corpuscles that can show keratinization and suggest squamous differentiation may be observed.^{5,11,12} The acinar cells and squamoid corpuscles have periodic acid-Schiff (PAS)-positive diastase-resistant granules. Acinar enzyme production is a common feature, and focal endocrine and ductal differentiation can occur.^{13–15} Osseous or chondroid metaplasia can be seen as well.^{5,16} Stromal elements may be present, and vascular and perineural invasion, calcification, necrosis, and frequent mitoses can be present.^{5,12,16} Immunohistochemical studies show staining with cytokeratin and evidence of acinar differentiation with reported positivity for lipase, trypsin, chymotrypsin, and alpha-1-antitrypsin. Some cells will stain with endocrine markers: neuron-specific enolase, synaptophysin, and chromogranin.^{5,12,17}

The differential diagnosis includes acinar cell carcinoma, pancreatic endocrine neoplasm, and solid and papillary epithelial neoplasm.^{5,12} There is significant overlap between the histopathological and immunohistochemical features of acinar cell carcinoma and pancreatoblastoma. Given the predominance of pancreatoblastoma in children and acinar cell carcinoma in adults, and the presence of similar genetic abnormalities in a significant percentage of these tumors, some believe that acinar cell carcinoma is the adult counterpart of pancreatoblastoma.^{5,18} Pancreatic endocrine neoplasms can be identified by cytology, lack of acinar differentiation, and presence of neuroendocrine differentiation.^{12,19,20} Solid and papillary epithelial neoplasms have papillary histologic features not present in pancreatoblastomas and, unlike pancreatoblastomas, do not stain for cytokeratin.^{12,21} Several authors have examined the ploidy and cytogenetics of pancreatoblastoma. In 1995 Akunne and associates reported the presence of diploid and tetraploid tumor cell populations, as well as translocations at t(13;22) and t(13;13) in a single case of pancreatoblastoma arising in a 4-year-old.²² Recently,

Abraham and coworkers examined nine pancreatoblastomas for mutations involved in embryonal malignancies, including β -catenin, adenomatous polyposis coli (APC), K-ras, chromosome 5q loss, and chromosome 11p loss. In their analysis they found the most common mutations were loss of chromosome 11p and alteration of the APC/ β -catenin pathway, seen in 86% and 67% of cases, respectively.¹⁸ The frequent loss of chromosome 11p ties the occurrence of pancreatoblastoma genetically with the Beckwith-Wiedemann syndrome, which is reportedly associated with abnormalities in the long arm of chromosome 11.²³⁻²⁵ The mutations in the APC/ β -catenin pathway are also seen frequently in hepatoblastomas and familial adenomatous polyposis (FAP), though there is only 1 reported case of pancreatoblastoma in an FAP patient. This analysis was also remarkable for the fact that there were no K-ras oncogene mutations, discriminating pancreatoblastoma from pancreatic ductal adenocarcinomas, in which the mutation is common.¹⁶

The radiologic characteristics of pancreatoblastoma have also been redefined. The largest study²⁶ analyzed the findings of 10 pathologically proven pancreatoblastomas that had been investigated by CT (10 cases), ultrasound (7 cases), and magnetic resonance imaging (MRI) (3 cases). It was observed that pancreatoblastomas were typically well-defined, heterogenous masses. In the 2 patients who received intravenous CT contrast, the tumors did enhance, and on MRI the tumors had low signal intensity on T1-weighted images and high intensity on T2-weighted images. Occasionally calcifications were seen, as was noted in our patient. In their series lobulations were relatively infrequent, though in two previous series of 6 patients lobulations were seen.²⁶⁻²⁹ Areas of necrosis can also be seen with these tumors.⁵ However, none of these radiologic findings are sufficiently characteristic to make a diagnosis of pancreatoblastoma.

Elevations in serum AFP, which were first noted in 1971,¹⁰ have lead to AFP levels being followed as tumor markers. AFP is commonly elevated in hepatoblastomas and yolk sac tumors. A Japanese series of 27 children with pancreatoblastoma found AFP levels in 15 of the patients to range from 30 to 138,000 ng/mL, with a median value of 910 ng/mL.³⁰ There does not appear to be any distinct correlation between AFP levels and outcome. In a French series of pancreatoblastomas, elevated serum AFP levels were noted in 4 out of 6 patients.² In their review they also noted that all patients reported in the literature except for 1 showed a decrease in AFP levels as the tumor responded to chemotherapy and elevations at recurrence. The chemotherapy regimens used to treat these patients varied greatly because there is no consensus on the optimal chemotherapy for these patients. In our patient, increased AFP levels did herald recurrent disease and decreased with tumor response to therapy.

Treatment of pancreatoblastoma consists primarily of surgical resection; chemotherapy and radiation therapy can also be effective in combination with resection. In a review by Defachelles and associates, 24 patients were identified who had had complete resection of their tumor, sometimes after neoadjuvant chemotherapy, and 21 of these patients were in complete remission.² In the series by Imamura and colleagues of 27 patients, 21 underwent resection and 14 of those patients were alive with a median follow up of 2 years.³⁰ Chemotherapy has been used as a neoadjuvant treatment in patients initially deemed unresectable and as adjuvant therapy. There is no defined chemotherapeutic regimen for these patients, mostly because of low numbers for study. Regimens that have shown a response include: cisplatin/etoposide/bleomycin,³¹ cisplatin/doxorubicin,³¹⁻³³ cisplatin/pirarubicin,³⁴ vincristine/cyclophosphamide/doxorubicin,³⁵ cisplatin/vincristine/cyclophosphamide/doxorubicin and cisplatin/vincristine/ifosfamide/doxorubicin,^{36,37} cisplatin/etoposide/pirarubicin/cyclophosphamide,³⁸ and cisplatin/etoposide.³⁹ Radiation therapy, both external-beam and intraoperative, have been used to treat pancreatoblastoma. Wu and Palosaari reported efficacy of a combination of external-beam radiation and intraoperative radiation in an unresectable tumor in an adult who did not respond to chemotherapy.⁴⁰ Murakami and colleagues also reported effective intraoperative chemotherapy in a child with locally recurrent pancreatoblastoma.³⁶ This was also seen in a report from Laramore and associates.⁴¹

Our patient initially responded to 5-FU in combination with external-beam radiation therapy followed by resection, and then had a 9-month response to the combination of vinblastine/ifosfamide/cisplatin. Pulmonary recurrences have been well-controlled with surgical resection and he continues to do well 9 years after diagnosis. Based on this one patient and responses by other patients to platinum-containing combination chemotherapy, regimens active in germ-cell neoplasms should be studied prospectively in patients with pancreatoblastoma.

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Review

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Pancreatoblastoma, initially known as “infantile pancreatic carcinoma,” was first described by Becker in 1957.¹ It is the most common pancreatic cancer in children, classified as an epithelial, nonendocrine neoplasm (Figure 1), with approximately 200 cases reported in the literature. Only a few cases have been reported in the adult population, in whom pancreatic cancers are among the most lethal, accounting for 27,000 deaths per year in the United States.² Pancreatoblastoma is a tumor characterized by a relatively good prognosis in children, but the prognosis becomes much more guarded in adulthood. Klimstra and colleagues compared the outcome of 9 affected children with that of 5 adults. They reported that overall 36% of the patients developed metastases, mostly to the liver. Of the adult cases, 3 of 5 died from disease, whereas only 1 of 6 evaluable children died. They also reported that good responses to chemotherapy were found only in the pediatric group.³

The fact that the patient presented in this review was not in the pediatric age range warrants concern. Even though surgical margins and lymph nodes were negative, he had several other factors that could adversely affect his outcome. These include nonresectable tumor at presentation, advanced stage, metastases post-resection, and initial involvement of the superior mesenteric vasculature.⁴ For these reasons, aggressive therapy was warranted.

The treatment of choice for pancreatoblastoma is complete surgical resection. Adjuvant chemotherapy and radiation have been helpful in treating initially nonresectable tumors, as was the case with the patient under discussion. There is no consensus supporting a first-line chemotherapy regimen. Responses have been reported with several chemotherapeutic agents including cisplatin, vincristine, doxorubicin, and cyclophosphamide.⁵ A Japanese study described the successful treatment of a 4-year-old girl with an initially massive nonresectable tumor using a neuroblastoma regimen consisting of pre- and postoperative administration of cyclophosphamide, etoposide, pirarubicin, and cisplatin.⁶ Defachelles and associates studied 7 cases of pancreatoblastoma and suggested that the treatment regimen should include cisplatin

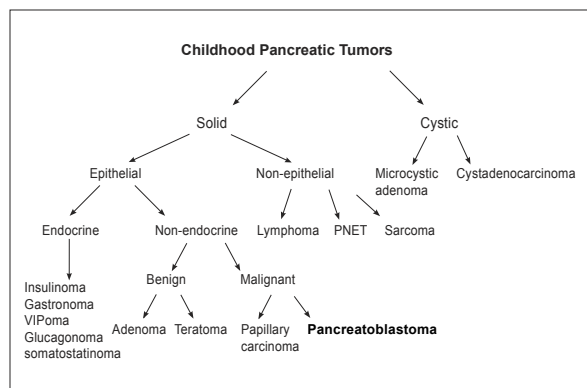


Figure 1. Derivative classification of endocrine, nonendocrine, benign, and malignant childhood pancreatic tumors.

and doxorubicin.⁷ In the case presented here, it seems that there was a favorable response to the cisplatin/ifosfamide/vinblastine combination.

Because of his adverse prognostic factors, this patient will need close follow-up. Shorter and colleagues suggested a fairly high recurrence rate of 60% for this type of tumor, even after complete resection.⁸ If another recurrence occurs in this case, other combinations of chemotherapy or higher doses than those already administered might be considered.

Measurement of serum AFP level seems to be an adequate marker for monitoring disease status. It has been reported to be elevated in up to 68% of patients with pancreatoblastoma.⁶ However, elevated AFP levels may not necessarily be consistent with recurrent disease.⁸ Other parameters including imaging studies and overall clinical status must also be considered in the follow-up management of this patient.

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