

## Pancreatoblastoma in Adulthood: Case Report and Literature Review

Rachel Thera<sup>1</sup>, Osama Souied<sup>3\*</sup>, Shahid Ahmed<sup>2</sup>, Kimberly Hagel<sup>3</sup>, Haji Chalchal<sup>3</sup>, Mussawar Iqbal<sup>3</sup>, Ronald Angeles<sup>4</sup>

<sup>1</sup>University of Ottawa, The Ottawa Hospital, Canada

<sup>2</sup>University of Saskatchewan, Saskatoon Cancer Center, Saskatchewan Cancer Agency, Canada

<sup>3</sup>University of Saskatchewan, Allan Blair Cancer Center, Saskatchewan Cancer Agency, Canada

<sup>4</sup>Department of anatomic pathology, Saskatchewan Health authority, Regina, SK, Canada

### ABSTRACT

**Background:** Pancreatoblastoma, a malignancy of the pancreas which primarily affects pediatric populations, is an aggressive and rare malignancy in adults aged 18 and older. Due to its rarity, there are a lack of treatment guidelines available to assist clinicians. Therefore, there is a need for further reporting of case studies of adult pancreatoblastoma. Here we present a case of metastatic pancreatoblastoma with extensive liver and peritoneal metastasis in an adult patient. We also present a literature review of 19 previously reported cases that were available in the English oncology literature over the past 30 years.

**Case Report:** A 44-year-old Caucasian male experienced a one-month history of abdominal pain, nausea, and vomiting. He was found to have pancreatoblastoma with peritoneal carcinomatosis and liver metastases. The patient was not a candidate for resection or palliative chemotherapy and therefore received supportive care only. Unfortunately, the patient died a few months after his diagnosis.

**Conclusion:** Adult pancreatoblastoma is a histologically varied and clinically aggressive entity. It presents a diagnostic and treatment challenge. Most patients experience local invasion or metastatic disease and the most common site of metastasis is the liver. Our case study represents the first case of metastatic peritoneal carcinomatosis associated with pancreatoblastoma recorded in the literature to date. Treatment success for some patients with pancreatoblastoma was achieved with surgical resection with or without adjuvant chemotherapy, although the overall prognosis of this malignancy is poor.

**Keywords:** Pancreatoblastoma; Adult pancreatic neoplasms; Pancreatic malignancy; Rare oncology; Oncology case report

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\*Corresponding author: Osama Souied. University of Saskatchewan, Allan Blair Cancer Center, Saskatchewan Cancer Agency, Canada

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### **Pancreatoblastoma in Adulthood: Case Report and Literature Review**

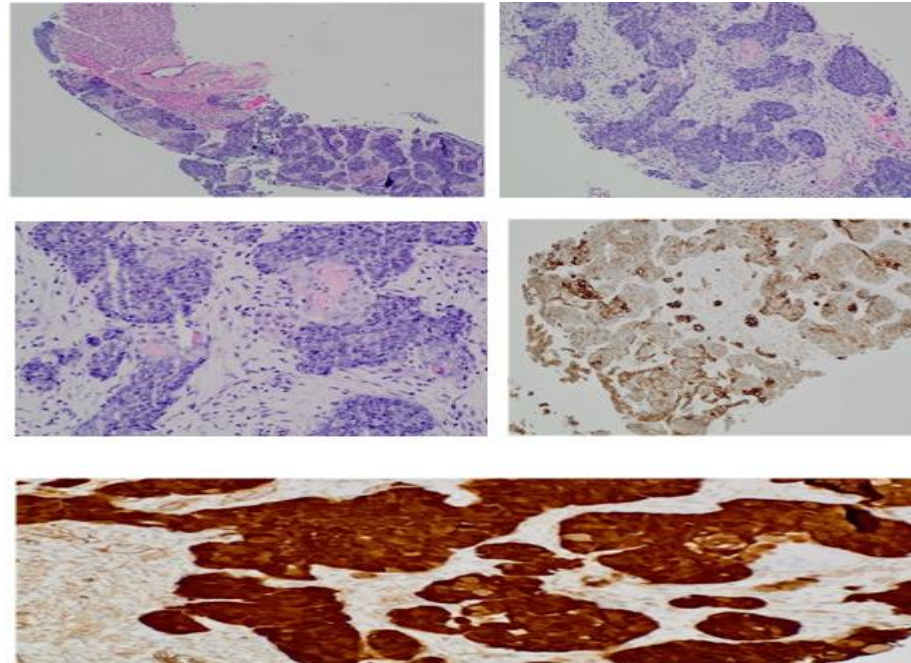
Although rare in pediatric populations, pancreatoblastoma is found even less commonly in adults.<sup>[1-3]</sup> This epithelial neoplasm occurs at a rate of 0.004 cases per 100,000 persons per year.<sup>[1-3]</sup> It accounts for approximately one percent of all pancreatic neoplasms.<sup>[1]</sup> The tissue composition of pancreatoblastoma is similar to the usual composition of the pancreas at 8 weeks gestation.<sup>[1]</sup> The pathognomonic histologic features for pancreatoblastoma include varying amounts of acinar, endocrine, squamous, and primitive components as well as squamoid corpuscles.<sup>[1,2]</sup> Clinically, pancreatoblastoma presents with features that result from mass compression. These include abdominal pain, palpable abdominal mass, weight loss, obstructive jaundice, and diarrhea most commonly.<sup>[1]</sup> Unfortunately, this means that patients do not become clinically ill until the mass reaches a large enough size to cause obstruction. As such, pancreatoblastoma is often metastatic upon diagnosis.<sup>[2]</sup> Due its aggressive nature, the prognosis for pancreatoblastoma is bleak, and considered to be much poorer than pancreatoblastoma of childhood.<sup>[1]</sup> Based on the available evidence to date, surgery is considered the only curative method of treatment and is associated with an average survival rate of 15 months.<sup>[2]</sup> The addition of chemoradiation after surgery may extend survival to 20.5 months.<sup>[2]</sup> Unfortunately, due to the rarity of the illness, and significant disease burden upon diagnosis, treatment options are limited.

In the current study, we present a case of metastatic pancreatoblastoma who exhibited symptoms for a month prior to his diagnosis. We report the important clinicopathologic features of the case along with our key findings and a literature review of previously reported cases, in 16 articles, over the past 30 years.

### **CASE REPORT**

A 44-year-old caucasian male presented to his general practitioner with symptoms of abdominal pain, nausea, and vomiting. He had a history of depression, anxiety, gastroesophageal reflux disorder, hypercholesteremia, and hypothyroidism. On physical exam he was found to be profoundly jaundiced, and had abdominal tenderness upon palpation.

He was sent for an ultrasound and found to have multiple hypoechoic lesions throughout the liver suspicious for metastasis. A CT scan demonstrated a primary mass in the body of the pancreas. The scan also demonstrated peritoneal carcinomatosis and multiple liver metastases. An ultrasound-guided biopsy of the liver was performed, and the pathology was found to be consistent with pancreatoblastoma. The major histologically defining feature was squamoid nests found within the tissue of the lesions. The primary tumor in the pancreatic body measured 4.3cm in diameter. The pathology was sent for a second opinion at the Mayo Clinic and the findings they reported were also consistent with pancreatoblastoma. Immunohistochemical staining of the tumor cells yielded positive results for keratin AE1/AE3, beta-catenin, CDX2, and synaptophysin. There was also positive focal and patchy staining for CK 5/6, p53, and p40 in the areas of the squamoid nests. The cells were negative for myogenin, S-100, and SOX10.



Figures 1-5

## **PATHOLOGY DESCRIPTION**

The liver biopsy shows infiltration by malignant poorly differentiated tumour (Figure 1). The tumour cells are arranged in nests separated by pale hypocellular stroma (Figure 2). The nests are composed of primitive appearing tumour cells with scant cytoplasm, hyperchromatic nuclei and abundant apoptotic bodies. There are many areas of squamoid nests (Figure 3). The tumour cells are positive for pankeratin AE1/AE3 (Figure 4), cdx-2 and focally for synaptophysin. The beta-catenin stain shows cytoplasmic and nuclear staining (Figure 5).

There is focal/patchy staining for CK5/6, p63 and p40 in the areas of squamoid nests. The pertinent negatives stains include TTF-1, pax-8, chromogranin, trypsin, GATA3, CK7, CK20 and NUT. Our pathologic diagnosis of pancreatoblastoma was confirmed by Mayo Clinic Laboratories on consultation.

The official diagnosis was reached one month after the onset of the patient's symptoms. His clinical status declined, and he was admitted to a local hospital for confusion likely secondary to his declining liver functions. His bilirubin was very high at 220 mg/dL. He was not a candidate for PTC (Percutaneous transhepatic cholangiogram) drain. At this point, he had lost 20-30 lbs over the previous two to three months. Unfortunately, the patient was ineligible for palliative chemotherapy due to his poor liver functions and performance status. The decision was made to proceed with supportive care only. The patient was followed by palliative care and eventually died of liver failure.

## **DISCUSSION AND LITERATURE REVIEW**

As adult pancreatoblastoma is a rare clinical entity, relatively few cases, approximately 40, have been reported in the previous literature.<sup>[1,3]</sup> The original name ascribed to this disease was infantile pancreatic carcinoma in 1957 and was later changed to pancreatoblastoma in 1977.<sup>[1]</sup> This was due to the observation that the abnormal cells of pancreatoblastoma histologically resembled the normal cells of a pancreas at 7-8 weeks gestation.<sup>[1,2]</sup> There are limited treatment options and the overall prognosis of adult pancreatoblastoma is poor, with the only potentially curative option being surgery.<sup>[1-3]</sup>

The literature search was conducted by the following process. Eighty entries from the Pubmed and Medline databases were identified when using the search term "pancreatoblastoma". These searches were limited to case studies, adults (age 18 and over), and from the years 1990-2020. After reviewing these articles for duplicates and relevance, 16 entries remained that were relevant to the current literature review. Reported in these 16 articles were 19 case studies on adults with pancreatoblastoma. Presented below is a succinct summary of the important clinicopathologic features of adult pancreatoblastoma to aid clinicians in the diagnosis and management of this condition. Table 1 encapsulates the key clinical features described in each case.

**Table1:** Relevant clinical features of each case report included in the literature review (N.R.= not reported; mets= metastases).

Study	Age/ Sex	Symptoms/ Duration	Tumor Site/Mets	Treatment	Response
Horens 1994	39/f	Mass/N.R.	Tail/none	Distal Pancreatectomy	Alive, 3 months without recurrence
Du 2003	78/f	Jaundice/ 3w	Ampulla of Vater/ invasion to duodenum	Pancreatoduodenectomy	Alive, 6 months without recurrence
Roosebrook 2004	29/f	None/0mo	Tail/None	Distal Pancreatectomy	N.R.
Rajpal 2006	50/ m	Abdo pain, early satiety, GI bleeding, pre-syncope/6mo	N.R./invasion to gastric wall	Multiple surgeries + chemotherapy	Deceased, 17mo after diagnosis
Ohike 2008	74/f	None/0mo	Intrabdominal cavity/mets to liver	Surgical resection	Alive, 9 years without recurrence
Cavallini 2009 (case 1)	26/ m	Abdo pain/N.R.	Head/none	Pancreatoduodenectomy	Alive, 51mo without recurrence
Cavallini 2009 (case 2)	69/ m	None/0mo	Body/none	Left pancreatoduodenectomy	Alive, 3.75mo without recurrence
Boix 2010	33/ m	Abdo pain/N.R.	Body/vascular and perinephric invasion	Left pancreatectomy and splenectomy with incomplete resection	Deceased, 97 days post operatively
Gringeri 2012	38/f	N.R./N.R.	N.R/Mets to liver	Pancreatoduodenectomy + chemo + cyberknife radiotherapy	N.R.
Salman 2013 (case 1)	60/ m	Abdo pain/2mo	Head/mets to liver	Hepatectomy, pancreatectomy + chemotherapy	Alive, initial full response. Mets 13mo after diagnosis
Salman 2013 (case 2)	51/ m	Jaundice, weight loss/N.R.	Head/vascular and perineural involvement and mets to one lymph node	Multiple surgeries + chemotherapy + chemoembolization	Deceased 51 months after operation
Salman 2013 (case 3)	58/f	Abdo pain/4mo	Tail/vascular and perineural invasion and 3 lymph nodes	Distal pancreatectomy	Alive, 30mo without recurrence
Hammer 2013	37/ m	Abdo pain,jaundice/N.R.	Head/mets to liver	N.R.	N.R.
Zhang 2015	30/f	Abdo pain, nausea,	Head/none	Surgical resection +	Alive, no recurrence

		vomiting/ N.R.		chemotherapy	
Vilaverde 2016	37/f	Abdo pain, fatigue/N.R.	N.R./ encasement of the superior mesenteric artery and celiac axis	Wedge resection	Deceased, 1 year after diagnosis
Chen 2018	26/m	Abdo pain, jaundice, weight loss/2mo	Head/mets to liver	Transarterial chemoembolization	Deceased, 4 years after diagnosis
Nunes 2018	31/m	Abdo pain, weight loss, diarrhea/1mo	Tail/mets to liver	Comfort care	Death, 3months after diagnosis
Terino 2018	34/m	Abdo pain, weight loss/4mo	Tail/mets to liver	Palliative Chemotherapy	N.R.
Liu 2020	49/m	Abdo pain/1mo	Tail/mets to liver	Surgical excision of pancreatic and hepatic lesions	Alive, 24mo without recurrence

### i) Demographic Characteristics

The mean age of patients in the case reports was 44.68 years with the range being 26-78. Eight of the case reports were of female patients and 11 were of male patients. This gives a male to female ratio of 1.57:1. The patient in our case report was male and his age was 44 years, the approximate mean calculated from the literature review, thereby fitting the prototypical demographic characteristics of patients with pancreaticoblastoma.

### ii) Clinical Findings

Abdominal pain, which is by far the most commonly reported symptom of pancreaticoblastoma, was reported in twelve out of 19 patients (63%). Most of these patients described abdominal pain in the epigastric region. Other reported symptoms including weight loss (21%), jaundice (21%), nausea/vomiting (5%), early satiety (5%), palpable mass (5%), diarrhea (5%) and fatigue (5%). Patients were symptomatic for an average of 1.9 months prior to their diagnosis. The patient reported in our case study experienced abdominal pain, nausea, and vomiting which is consistent with the previous literature.<sup>[1-9]</sup> On careful observation our patient experienced abdominal pain, visible jaundice, nausea, and vomiting initially. Over the course of a few months, weight loss became apparent as another clinical feature of his illness. Therefore, he experienced all the major reported symptoms of pancreaticoblastoma.

Most patients in the case studies had locally invasive disease or metastases at the time of diagnosis. Six (31%) of patients were found to have only a primary mass of the pancreas. Four (21%) of the patients were found to have locally invasive tumors at the time of diagnosis. Most patients in this group had vascular and perineural invasion. However, some of the patients had invasion of their tumor into the duodenum. Nine patients (47%) had already metastases on diagnosis. The

patient in our case study experienced metastases to the liver as is typical of most patients with pancreatoblastoma. Seven of the nine patients with metastatic disease had metastases to the liver (67%). Two patients had metastatic spread to lymph nodes. The lungs are another site of metastasis reported in the literature. None of the patients included in these case reports had lung metastases at diagnosis, however, one patient experienced metastasis to the lungs, 37 months after surgical treatment of his pancreatoblastoma.<sup>[4]</sup> A novel finding in our patient's case was the presence of metastatic peritoneal carcinomatosis which was not presented in any of the reviewed case studies. To our knowledge, our case study is the first report of a patient with pancreatoblastoma with peritoneal carcinomatosis.

### iii) Imaging Findings

Ultrasound and CT were the primary imaging modalities used in evaluation of tumor location, size, and characteristics. In some cases, MRI was used to provide further information about the tumor. The average mass size was 6.0cm and the size ranged between 1.3cm and 13.0cm. Equal amounts (32%) of patients had tumors that were located in the head and tail of the pancreas. There were two (11%) patients who had masses in the pancreatic body. This was also the location of tumor in the patient described in our case report. One patient (5%) had a tumor arising from the Ampulla of Vater. In two case reports,<sup>[8,10]</sup> the location of the primary mass was not reported and in one case, the primary location was unclear as the mass appeared to be intrabdominal but adhered to the pancreas.

### iv) Pathological Features

As noted in previous literature and throughout the case reports, the identifying features of pancreatoblastoma are acinar differentiation and areas of squamoid nests.<sup>[1-3]</sup> It is very similar to acinar cell carcinoma, except for the squamoid nests which are the key differentiating feature.<sup>[2,3]</sup> These nests are comprised of plump and whorled cell groupings, sometimes referred to as islands. These cells contain eosinophilic cytoplasm and clear nuclei.<sup>[1-3]</sup> Another differentiating feature of pancreatoblastoma is that it may contain areas of other cell lines including neuroendocrine, ductal, primitive components, or a combination of the aforementioned types.<sup>[3]</sup> Acinar cell carcinoma generally does not contain these features.<sup>[3]</sup> Please see **Table 2** for a comparison of the differentiating features of pancreatoblastoma and other similar pancreatic neoplasms. Due to the varied histologic components of pancreatoblastoma, it may be difficult to diagnose prior to surgical resection.<sup>[3]</sup>

Immunohistochemical staining of pancreatoblastoma cells depends on the cell line differentiation of the sample. Neuroendocrine components may stain positively for chromogranin and synaptophysin.<sup>[3,11]</sup> The ductal components stain positively for CK7 and CK9.<sup>[1,3]</sup> Finally, the acinar components generally stain positive for trypsin and chemotrypsin.<sup>[1,3]</sup>

In the majority of cases of adult pancreatoblastoma, the tumor markers are within normal range.<sup>[1]</sup> However, in children CEA and AFP have found to be elevated. CA19-9 has been reported to be elevated in some patients with adult pancreatoblastoma.<sup>[1,3]</sup> There have also been reports of AFP positivity in the epithelial component of pancreatoblastoma.<sup>[1]</sup>

#### **v) Treatment**

As previously stated, the only potentially curative treatment method for pancreatoblastoma is surgical removal.<sup>[1]</sup> As such, surgery is the preferred treatment modality. Adjuvant chemoradiotherapy may provide additional survival benefit and may also be considered.<sup>[1-3]</sup> Of the patients described in the case reports, 15 (79%) patients in total underwent surgery. Ten (52%) patients were treated with surgery alone. Surgical methods primarily included wedge resection, pancreatectomy, or pancreatoduodenectomy. Some patients also received a splenectomy or partial hepatectomy. The other five patients (26%) received adjuvant chemotherapy. One patient also received adjuvant chemoembolization. Another patient received cyberknife radiotherapy in addition to surgical resection and chemotherapy. One patient received transarterial chemotherapy (TACE) alone. Only one patient received chemotherapy alone. Another patient received comfort care only, as was the treatment provided for the patient in our case report due to his significant disease burden the time of diagnosis. His liver function was unfortunately too poor, and he was unable to tolerate palliative chemotherapy.

Chemotherapy regimens previously described in the literature include a combination of gemcitabine, cisplatin and doxorubicin.<sup>[2,3]</sup> There were multiple chemotherapy regimens described in the case studies, however, there did not appear to be a clear pattern on the type provided for the patients. One patient included in the review received a regimen of cisplatin, vincristine and bleomycin.<sup>[5]</sup> Another patient received doxorubicin and carboplatin. Two patients received cisplatin and doxorubicin. One of these patients was later switched to docetaxel and gemcitabine due to lack of a response on the initial therapy. This new regimen also displayed a lack of benefit for the patient who was then switched to capecitabine and oxaliplatin. This treatment was not tolerated well and ultimately the patient died from disease progression.<sup>[6]</sup> This demonstrates the lack of consensus regarding chemotherapy.



**vi) Prognosis**

Due to the aggressive nature of the disease and the late onset of symptoms in the course of the illness, the prognosis of pancreatoblastoma is poor.<sup>[1-7,12]</sup> The majority of the patients included in the review were still living at the time of publication of the studies. There were 8 out of the 19 (42%) patients that were alive without recurrence. One patient (5%) was alive with significant metastases. Six patients (32%) were deceased from the burden of their disease. The average survival time after diagnosis was 22 months for patients who were deceased at the time of publication of their case reports. There was a significant outlier, however, with a patient who was still in remission 9 years after their initial treatment.<sup>[12]</sup> The treatment methods for the individuals were varied for the patients who were deceased. Two patients underwent surgery alone, 1 patient underwent surgery and adjuvant chemotherapy, 1 patient underwent surgery, chemotherapy, and radiation, and 1 patient received comfort care. Of the patients who were still living, 7 underwent surgery alone and two underwent surgery and chemotherapy. Conclusions cannot be drawn at this time regarding treatment efficacy based on these numbers. It is possible that the patients who died presented with greater disease progression or tumors that were too technically difficult to resect. All of the patients who died either had local invasion (50%) of the tumor or metastases (50%).

**vii) Differential Diagnosis**

The differential diagnosis for pancreatoblastoma include pancreatic neuroendocrine tumor (NET), acinar cell carcinoma, and solid-pseudopapillary neoplasm.<sup>[1,2]</sup> Please refer to **Table 2**. For a review of the differentiating features of these diagnoses. Understanding of the differentiating features of these disease entities may lead to swifter diagnosis and timely appropriate treatment.

**Table2:** This table describes the relevant features that differentiate pancreatoblastoma from other similar pancreatic neoplasms. This chart is adapted from Nunes et al.<sup>2</sup> and the information is from reviews by Nunes et al.<sup>[2]</sup>, Chen et al.<sup>[1]</sup>, Sun<sup>[17]</sup>, and Young<sup>[18]</sup>

Criteria	Pancreatoblastoma	Acinar Cell Carcinoma	Pancreatic NET	Solid-pseudopapillary Neoplasm
<b>Clinical</b>				
Age	Young	Older	Older	Young
Sex	Male Predominant	Male Predominant	Male Predominant	Female predominant
Symptoms	Abdominal pain, jaundice, weight loss	Nonspecific symptoms	Variable, but most symptoms result from obstruction-Abdominal pain and jaundice	Nonspecific, often incidental finding

Histopath				
Nuclei	Variable, but they are clear within the squamoid nests	Round to oval	Round to oval	Uniform grooves with small nucleoli
Cytoplasm	Variable, but in the squamoid nests, it is eosinophilic	Granular, dense, and well-defined	Clear, oncocytic, wispy, scant	Scant with tail like inclusions
Stroma	Variable	Vascular	Vascular	Mucinoid fibrovascular
Architecture	Squamoid nests or islands	Single cells, stripped nuclei, grape like clusters. No squamoid nests or hardly visible ones.	Single cells, loose clusters, pseudo-rosettes. No squamoid nests.	Single cells and papillary fronds. No squamoid nests.
CK AE1/AE3	Positive	Positive	Positive	Positive
Neuroendocrine markers	Focally positive if neuroendocrine components present	Negative	Positive	Negative
B-Catenin	Focally positive	Negative	Negative	Positive

## CONCLUSION

Adult pancreatoblastoma is an uncommon and aggressive malignancy.<sup>[1-4]</sup> Patients often do not experience symptoms until the tumor burden has been large enough to cause obstruction or compression of surrounding tissues.<sup>[1]</sup> As such, adult pancreatoblastoma is often advanced when detected, which in turn means it generally has a poor prognosis. Treatment decisions can be challenging regarding this specific neoplasm, as firm guidelines have not been established due to its rarity. However, surgical resection, with adjuvant chemotherapy's uncertain benefit, appears to be the best treatment modality.

## CONSENT AND APPROVALS

This case study was exempt from Research Ethics Board review. Approval was sought from the Data Access Committee at the Saskatchewan Cancer Agency to access the patient's record for the purpose of conducting the review.

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## CONFLICTS OF INTEREST

The authors declare no conflict of interest regarding this article.

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