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Case Report Open Access

Pancreatoblastoma in an Adult Patient with Late Recurrence

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Abstract

Pancreatoblastoma (PB) is among the most frequent pancreatic tumor in childhood, but exceedingly rare in adults. The prognosis of PB in adults is very poor with a mean survival time of 10 months.

The case describes a 36-year-old woman with a painful palpable tumor in the upper part of the abdomen. The complete resection of the tumor confirmed a 14 cm well-circumscribed tumor with heterogeneous morphological appearance with three main components – neuroendocrine, acinar and squamous. The morphologic and immunohistochemical features proved to be consistent with PB. The patient did not receive any adjuvant chemotherapy. Seventy-two months later a bulky relapsing abdominal tumor was discovered. The histology revealed undifferentiated tumor with solid sheets of medium large atypical cells, areas of tumor necrosis and high mitotic index. Despite the different morphology in the relapse, neuroendocrine differentiation was documented with immunohistochemistry.

The case presents a rare malignant tumor of the exocrine pancreas in adult patient. The discussion focuses on the characteristic macroscopic and histological characteristics, immunohistochemical profile and molecular genetics, considering a list of common differential diagnostic entities. This study underlines the importance of recognizing the pancreatoblastoma as a malignant tumor in non-paediatric group in which surgical resection is the best choice of treatment, associated with long-term survival.

Introduction

Pancreatoblastoma is a rare malignant tumor of the pancreas originally reported by Bohn in 1885 [1]. The histological resemblance of the tumor to fetal pancreatic tissue led Horie to propose the term "pancreatoblastoma" in 1977 [2]. Pancreatoblastoma is most frequently occurring in the first 10 years of life with a median age of 5 years at presentation and a slight male predominance [3]. The incidence in adults is very low, with less than 40 cases reported in the literature [3]. The median age of adults is 37 years (range, 18–78 years), and men and women are equally affected. Apart from surgical resection, optimal treatment has not been established. Chemotherapy and radiotherapy may have a role in recurrent, residual, unresectable and metastatic disease but the published data are limited [3]. The outcome in children is more favourable than in adults. The longest survival time reported, following resection in a child was 28 years and an adult with pancreatoblastoma was 9 years [4].

In this report we describe a case of pancreatoblastoma in an adult female patient with a late recurrence 72 months after the primary tumor resection. The clinical presentation, morphological diagnostic criteria and treatment options have also been discussed.

Case Report

A previously healthy 36-year-old woman presented with abdominal pain and a palpable tumor in the upper part of the abdomen. The levels of carcinoembryonic antigen (CEA), neuron-specific enolase (NSE), ferritin, CA199, CA125, CA242, and α-fetoprotein were within normal ranges. The chest x-ray was unremarkable (Figure 1). Abdominal ultrasound and computer tomography (CT) demonstrated a 109 × 117 mm encapsulated solid homogeneous tumor in the pancreatic tail with small cystic areas (Figure 1a). On CT, the primary tumor showed lower attenuation than liver tissue, with mild heterogeneous contrast enhancement. With a tentative diagnosis of solid pseudo-papillary tumor or mucinous cystic tumor of the pancreas the patient underwent diagnostic laparotomy with complete resection of the tumor.

The resection specimen revealed a 14 cm large, well-circumscribed tumor in the tale of the pancreas. The cut surface was yellowish and fleshy with small cysts. Microscopically, the tumor had heterogeneous morphological appearance with three main components (Figure 2a through 2c). The major tumor component was composed of large geographic nests of monotonous-appearing cells, separated by dense, fibrous septa, some of which contained atrophic pancreatic lobules and residual ducts. The neoplastic cells in those areas had basophilic nuclei and scant cytoplasm, suggestive for "neuroendocrine" differentiation (Figure 2b). In addition there were scarce areas, in

which the cells mimicked pancreatic acinar differentiation with vaguely granular, amphophilic cytoplasm, central nuclei and prominent nucleoli. Focally, small collections of cells with squamoid appearance, composed of polygonal cells with abundant eosinophilic cytoplasm, well-delineated cell borders and focal keratinization represented the third histological type (Figure 2c). Mitotic figures were scattered throughout the tumor and small areas of tumor necrosis were observed. There was no record of vascular and/or perineural infiltration.

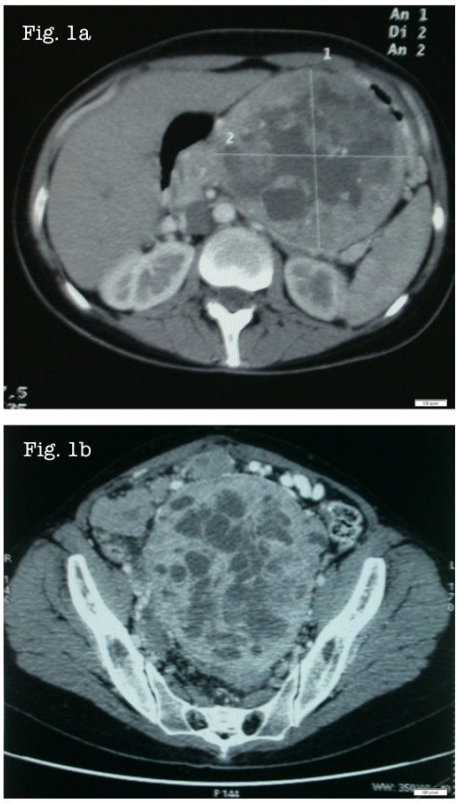

Figure 1: Computer tomography images: a) The first CT scan demonstrating large multicystic mass in the pancreas. b) CT scan of the recidive demonstrating a large inoperable abdominal tumor.

The various morphologic components of the tumor were also immunohistochemically distinct. The neuroendocrine component was positive for CD56 (Figure 2d), synaptophysin (Figure 2e) and chromogranin. The ductal component stained with antibodies against cytokeratin 8 and cytokeratin AE1/AE3. Focal positivity was observed with antibodies CAM 5.2 and BER-EP4. Cytokeratin 5/6, cytokeratin 14 and cytokeratin 19 as well as CDX-2 and CEA were negative. Ki67 showed low proliferation index below 5%. The final diagnosis of pancreatoblastoma was made on the basis of these morphological and immunohistochemical features.

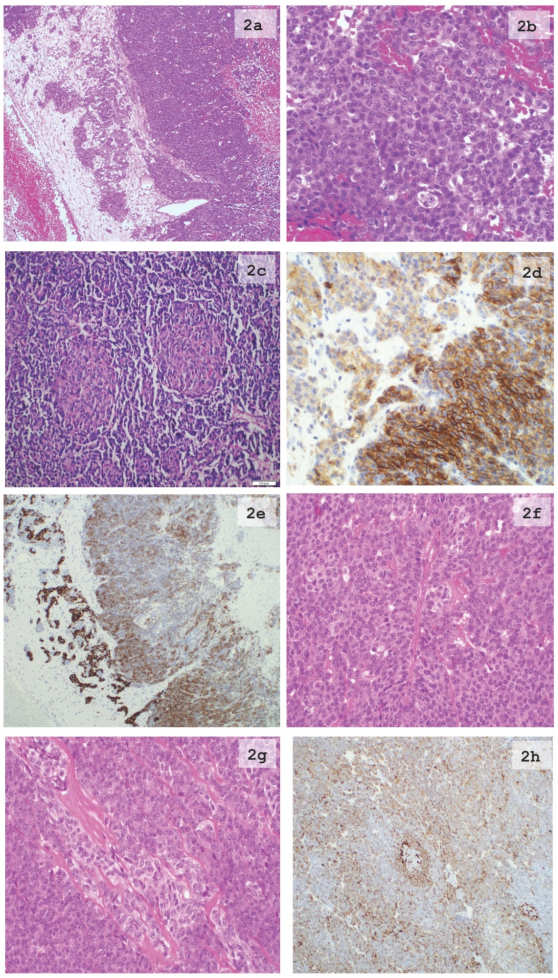

Figure 2: Microscopic and immunohistochemical images from the primary tumor and recurrence. 2a: Low magnification of the tumor showing heterogeneous picture with different areas from the tumor with haemorrhages, small microcystic spaces and degenerative changes (H&E section magnification 10X). 2b: H&E section with solid proliferation of small atypical cells with round nuclei with "salt and pepper" chromatin and relative scarce eosinophylic cytoplasm (magnification 40X). 2c: H&E section demonstrating two squamoid bodies and partially proliferation of small cells with hyperchromatic nuclei and scant cytoplasm (magnification 20X). 2d: IHC staining with anti-CD56 antibody demonstrating strong membranous staining in the solid areas and weak focal, partial membranous staining in the acinar areas (20X). 2e: IHC staining with anti-Synaptophysin antibody demonstrating relatively weak staining in the solid areas and strong cytoplasmic staining in the acinar areas (10X). 2f: H&E section demonstrating solid proliferation and small microcystic spaces of small cells with hyperchromatic nuclei and scant cytoplasm (magnification 40X). 2g: H&E section showing different areas from the tumor with trabecular and microacinary growth pattern (magnification 40X). 2h: IHC staining with anti-Synaptophysin antibody demonstrating moderate diffuse staining in the solid areas (10X).

The postoperative course was unremarkable, and the patient was dismissed 2 weeks after surgery. Fifty-four months after the primary diagnosis, the CT scan detected relapsing tumor mass, localized in the pancreas with extension towards the liver, compression of the blood vessels in the area, followed by portal hypertension and subsequent hepatosplenomagaly. At this stage, the patient would refuse adjuvant therapy. The next CT, performed 72 months after the first operation, revealed a very advanced stage of the disease, with lymph node and haematogenous metastases (liver and adrenal gland), large tumor in the liver hilum, compression of inferior vena cava and dilatation of the two kidney veins together with venous thrombosis below the kidney veins (Figure 1b). The abdominal tumor was occupying the entire pelvic area. Biochemistry tests and tumor markers were within normal ranges with exception of slightly elevated α-fetoprotein of 8.0 ng/ml (reference values<6.0 ng/ml). At this stage, it was decided to perform a palliative resection to reduce the tumor burden.

The gross specimen consisted of large fragmented tumor with pink-grey cut surface and heterogeneous consistency. Multiple tissue blocks revealed a uniform picture with solid sheets of medium large atypical cells with vesicular nuclei, prominent nucleoli and more abundant cytoplasm (Figures 2f and 2g). The vague focal appearance of the cells was suggesting an acinar differentiation. There were large areas of tumor necrosis and high mitotic index. The same panel of immunohistochemical markers confirmed that the tumor retained neuroendocrine differentiation with diffuse, uniform expression of CD56, synaptophysin and chromogranin A (Figure 2h). There was detected a weak focal expression of CAM 5.2 and BER-EP4 and the proliferation index assessed by Ki67 was below 3%.

Discussion

Pancreatoblastoma (PB) is an uncommon malignant epithelial neoplasm with <200 cases reported in the literature. It represents approximately 0.5% of all exocrine tumors of the pancreas. PB is one of the most frequently paediatric pancreatic neoplasms, accounting for approximately 25% of pancreatic tumors occurring in the first decade of life [3]. Exceptionally, PB can arise in adults [5-25]. The incidence in adults is very low, with less than 40 cases reported in the literature [3]. The median age of adults is 37 years (range, 18–78 years), and men and women are affected with nearly the same frequency. Rare congenital cases, associated with Beckwith-Wiedemann syndrome or familial adenomatous polyposis (FAP) have also been described [15]. In adults, PB tends to be more often symptomatic than in children. The most common symptoms and signs are either nonspecific gastrointestinal symptoms - abdominal pain and weight loss, or obstructive jaundice, diarrhea, and a palpable mass [3,5]. Serum markers are generally not helpful in the diagnosis of PB. Significantly elevated serum levels of CEA and/or a-fetoprotein level have been reported in 30-50% of paediatric cases, though they are not usually high with adult pancreatoblastoma patients [9,17,22,26]. Elevated serum levels of tumor markers at diagnosis, usually fall down to normal after the tumor resection and serve as potential indicators of subsequent tumor recurrence.

PB is typically a slow growing large well-circumscribed tumor, ranging between 2 and 20 cm (mean 11 cm) [5,10,25].

Pathology findings, immunohistochemistry and molecular alterations of PB

Macroscopically, most PBs is well circumscribed, partially encapsulated tumors [25]. The cut surface is grey or tan with a soft consistency, and often exhibits intratumoral haemorrhage and/or ischemic necrosis.

Microscopically PB is defined as a primary malignant neoplasm of pancreas, manifesting both exocrine and endocrine differentiation with an organoid pattern containing lobular structures with squamoid corpuscles and the presence of acinar cells with zymogen granules [3]. The tumor is organized into nests of primitive-appearing cells separated by dense, variably cellular stromal bands. There can be a variety of components, including those with neuroendocrine differentiation, ductal differentiation, and even heterologous elements, such as bone and cartilage. The most characteristic histologic finding, and a diagnostic hallmark to the correct diagnosis, is the presence of squamoid corpuscles. These appear as variably sized foci of squamoid cells, with occasional keratinization. They can be subtle and difficult to detect, or they can appear overtly squamous. Evidence of an endocrine component, acinar cells containing zymogen granules and the presence of α-fetoprotein suggest that this neoplasm arises from multipotential stem cells with great similarity to the microscopic pattern of acinar buds during pancreatic development at the eighth week of embryogenesis [2,3]. The possible mechanism, suggested by Horie is that malrotation or lack of fusion of the ventral pancreas at the seventh week may result in developmental disturbance with persistence of the foetal pancreatic acinar buds, remaining at the developmental level of the eighth week. Thus, the embryonal viability of the isolated pancreatic tissue may acquire later on growth potential and give rise to PB. The squamoid corpuscle might originate in pluripotential epithelial cells from pancreatic primordial, which are precursors of duct cells showing squamous metaplasia [2].

Immunohistochemistry: In his original description Horie suggested that PB displays exocrine differentiation [2]. Later it was proposed that the tumour manifests both exocrine and endocrine differentiation [27]. Histochemical and ultrastructural studies have shown that some PBs have both exocrine and endocrine components associated with both zymogen and neuroendocrine granules, sometimes in the same cells, or in different cells [27]. In addition to pan-cytokeratin and cytokeratin 8 expression, PB usually exhibits neuroendocrine differentiation based on immunohistochemical detection of neuroendocrine markers (chromogranin, neuron-specific enolase or synaptophysin) as well as insulin, gastrin, somatostatin, AFP, α-1-antitrypsin, CEA and keratin [28]. According to one study, the characteristic squamoid corpuscles were positive with simple epithelia type cytokeratins 8, 18 and 19 and were lacking well-developed desmosome-tonofilament complexes - a fact undermining the hypothesis that these cells show characteristics of squamous metaplasia [29]. In some studies, aberrant patchy nuclear and cytoplasmic β-catenin expression, as well as Cyclin D1 expression was demonstrated particularly in the squamoid corpuscles, but not in the areas with acinar differentiation [15,30]. It was proposed that the aberrant β-catenin expression might be related to the morphogenesis of the squamoid corpuscles [30]. There are only sporadic data with regard to proliferation index in PB [30]. In the case study both the primary tumor and the recurrence showed low proliferation index, assessed by Ki67. Despite the low proliferation, high mitotic index was observed in the relapsed tumor. Discordant mitotic index/Ki67 proliferation index was observed both in gastrointestinal

neuroendocrine tumors and breast tumors [31,32]. The two techniques look at somewhat different parameters: the Ki67 proliferative index is the percentage of cells proliferating, whereas the mitotic rate is determined as proliferating cells per unit area [31]. Another hypothesis is that the apoptosis might be the explanation for the discrepancy between Ki67 and the mitotic count in some breast cancers [32]. In general, immunohistochemistry does not usually contribute to the diagnosis of pancreatoblastoma.

Molecular findings: Due to the fact that most of PB cases are published as single case reports, the molecular pathogenesis of the disease has not been investigated in depth. The most frequent reported abnormalities are of chromosome 11p15.5 (locus also affected in children with Beckwith-Wiedemann syndrome), associated with alterations in the Wnt signalling pathway [3,15,33]. In addition somatic alterations in the adenomatous polyposis coli (APC)/β-catenin pathway were also detected in PB [15]. Those molecular findings indicate similar molecular pathogenic mechanisms in the development of PB and hepatoblastomas [15].

Differential diagnosis: The correct diagnosis of PB in adults might be a diagnostic challenge due to both histologic heterogeneity and the low frequency of the disease. Commonly considered differential diagnostic entities include acinar cell carcinomas, pancreatic endocrine neoplasms, poorly differentiated adenocarcinomas, and solid pseudopapillary tumors (SPT).

Pancreatic endocrine neoplasms (PEN) may pose potential diagnostic problem. Both PEN and PB are composed of geographic nests of monotonous-appearing cells, separated by dense, fibrous septa. Adding to the confusion, PB often contains a neuroendocrine component of different size, positive for neuroendocrine markers CD56, synaptophysin and chromogranin. The main PEN distinctive features remain the monotonous proliferation of medium large cells with scant cytoplasm and characteristic "salt-and-pepper" chromatin pattern, and the lack of other cell types, such as ductal or acinar cells or squamoid corpuscles, which are present in pancreatoblastoma. The immunohistochemical "dot-like" cytokeratin staining pattern is diagnostic for PEN. On the other hand, chymotrypsin or trypsin expression might be helpful in identifying the acinar component in PB.

PB cases with abundant acinar cell differentiation might be difficult to distinguish from acinar cell carcinoma. The acinar cell carcinoma shows either acinar growth pattern with small glandular units with numerous small lumina within each island of cells giving a cribriform appearance or solid growth pattern with solid nests of cells lacking luminal formations. Within these nests, cellular polarization is generally not evident. Acinar cell carcinomas lack neuroendocrine differentiation and squamoid corpuscles, which are a hallmark of PB.

SPT can sometimes present a diagnostic challenge. Macroscopically, SPTs are large, solitary, encapsulated masses, similar to pancreatoblastoma. Occasionally, SPTs may show solid monomorphic pattern with variable sclerosis or a pseudopapillary pattern. The neoplastic cells are uniform polyhedral cells, arranged around delicate, often hyalinised fibrovascular stalks with small vessels. Luminal spaces are consistently absent. Often in the solid parts, disseminated aggregates of neoplastic cells with foamy cytoplasm or cholesterol crystals surrounded by foreign body cells may be found. The hyalinised connective tissue strands may contain foci of calcification and even ossification. The neoplastic cells have either eosinophilic or clear vacuolar cytoplasm. The most consistently positive markers for SPN are alpha-1-antitrypsin, alpha-1-antichymo-trypsin, neuron specific enolase (NSE), vimentin and progesterone receptors.

Ductal adenocarcinoma rarely comes as a differential diagnostic entity because it is substantially different from PB both clinically and histologically. PB are slow-growing, often found incidentally or in association with nonspecific symptoms, whereas ductal adenocarcinomas commonly occur with jaundice and weight loss, and are much smaller than PB at presentation. Histologically, PB can have a tubular component, yet it is present in a small percentage of the tumor. In contrast to ductal adenocarcinoma, the cytological appearance of the epithelium lining the tubules in PB is low grade, and the desmoplastic stroma typical for adenocarcinomas is generally absent.

Clinical symptoms at presentation	
Abdominal pain	41%
Abdominal tumor	24%
Obstructive jaundice	21%
Weight loss	26%
Diarrhea	12%
Incidental finding	6%
Location of the primary tumor	
Head of the pancreas	35%
Tail of the pancreas	14%
Body of the pancreas	21%
Advanced disease	12%
Metastasis	
Lymph nodes	15%
Liver	27%
Pleura and lung	6%
No evidence of metastasis	38%
Treatment	
Surgical resection	44%
Surgery+chemotherapy	30%
Surgery+radiotherapy and chemotherapy	18%
Follow-up	
Alive, NED	35% (follow-up 5-108 months)
Alive with metastasis	6%
Dead of the disease	35% (1-26 months)

Table 1: Characteristic features of adult pancreatoblastoma (literature data from 34 patients).

Treatment and prognosis: PB is an aggressive disease, and adults affected by PB have shorter long-term survival than children (Table 1). More than 50% of the patients described to date died of disease within

a 3-year follow-up period [3,5]. The reported mean survival time for adults is 10 months (Table 1). In contrast, in paediatric patients without evidence of metastatic disease at time of presentation, a combination of surgery and chemotherapy is a matter of choice, giving excellent results. In paediatric patients with metastasis, however, the outcome is also poor, with a mean survival period of 1.5 years. At present, the only treatment ensuring long-term survival is the radical surgical resection. Of the 34 adult cases reported in the literature, 33% had distant metastases at presentation. 94% underwent surgical resection and 42% were alive with a medium follow-up of 34 months (5-108 months) and 36% died of the disease [5-25,28,34,35]. The mean survival period for adults dying of tumor was 15.2 months. After surgery, the role of adjuvant therapy is unclear and it is based on few reports (Table 1), although some authors have strongly recommended adjuvant chemotherapy because of the metastatic potential of the tumor. So far the golden standard of treatment for pancreatoblastoma is complete surgical resection, which may require pancreaticoduodenectomy or total pancreatectomy, depending on the size and location of the tumor. The role and efficiency of adjuvant therapy (chemotherapy and/or radiotherapy) still remain unclear.

Conclusion

A healthy 36-year-old woman with abdominal pain underwent a complete laparoscopic resection of large encapsulated solid homogeneous tumor in the pancreatic tail. Microscopically, a heterogeneous malignant tumor, composed of large areas with neuroendocrine differentiation, zones of acinar differentiation and focal areas with squamoid corpuscles, was discovered. This histological picture and the ancillary expression of neuroendocrine markers CD56, chromograninA and synaptophysin supported the diagnosis of pancreatoblastoma. Seventy-two months after the primary tumor resection the patient died with large unresectable relapsing tumor with multiple lymph node and haematogenous metastases.

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