

Review Article

Pediatric Neoplasms of the Pancreas: A Review

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Abstract

In infants and children, pancreatic neoplasms occur uncommonly. Histologically, these tumors can resemble pancreatic embryonic elements or more well-differentiated pancreatic structures, in a subset the cellular origin can't be delineated. This review discusses three of the most classic pediatric pancreatic neoplasms: pancreatoblastoma, solid pseudopapillary neoplasms and pancreatic endocrine neoplasms. These tumors can be a manifestation of a syndromic process and genetic aberrations have been linked to a subset of these neoplasms, as discussed in this paper.

ABBREVIATIONS

PEN: pancreatic endocrine neoplasms, SPN: Solid pseudopapillary neoplasms, mTOR: mammalian target of rapamycin, PI3K: phosphatidylinositol 3 kinase, AKT: protein kinase B, EXPeRT: European cooperative study group for pediatric rare tumors, SEER: Surveillance, Epidemiology and End Results, LOH: loss of heterozygosity, BWS: Beckwith-Wiedemann syndrome, DAXX: death-domain associated protein, ATRX: alpha thalassemia/ mental retardation syndrome X-linked, VEGF: vascular endothelial growth factor

INTRODUCTION

Pancreatic neoplasms in infants and children occur uncommonly. The North American population-based Surveillance, Epidemiology and End Results (SEER) registry examination from 1973-2004 showed an incidence of 1.8 cases per 1,000,000 for pediatric pancreatic tumors in the United States. Females outnumbered males 1.9:1, and Asians demonstrated the highest incidence. Both female gender and surgery have been identified as independent predictors of improved survival [1].

It is important to be familiar with the histopathologic and clinical features of these tumors. These tumors may be the first manifestation of a genetic syndrome or could occasionally present with life-threatening symptomatology. Additionally, they need to be properly characterized and distinguished from the more common, metastatic tumors to the pancreas.

Complete surgical resection is the optimal treatment for most primary pancreatic neoplasms. As their genetic basis is further elucidated, targeted medical therapies may be utilized to treat cases of metastatic disease or when a total resection cannot be performed.

Three of the most common primary pancreatic neoplasms of children are reviewed here: pancreatoblastoma, solid pseudopapillary neoplasm of the pancreas and pancreatic endocrine neoplasms. The clinical and histopathologic

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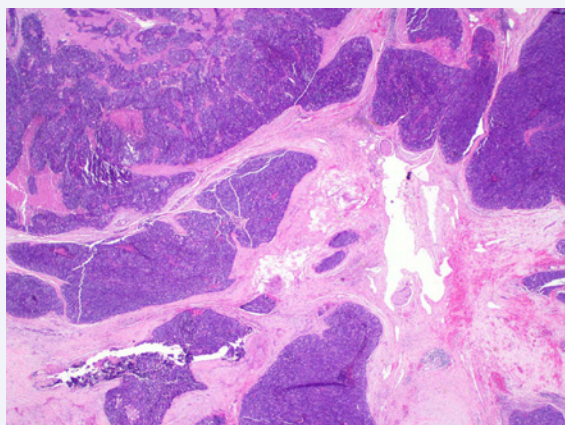
- Pediatric
- Pancreas
- Pancreatoblastoma
- Solid
- Pseudopapillary
- Neoplasm
- Pancreatic endocrine neoplasm

features are discussed, along with an update of the molecular pathogenesis of these tumors. When available, the pediatric-related perspective of these neoplasms, as they may differ from the adult population, is also discussed.

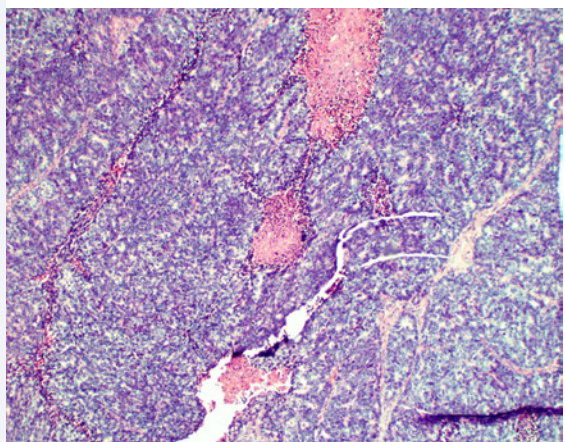
PANCREATOBLASTOMA

Pancreatoblastoma, first described in 1957 by Becker, is the classic embryonic neoplasm of the pancreas, with the tumoral tissue recapitulating the embryonic elements of the pancreas. The tumor arises from multipotential stem cells and is analogous to other embryonal neoplasms including Wilms tumor and hepatoblastoma. A report from the European cooperative study group for pediatric rare tumors (EXPeRT) in 2011 by collecting 20 registered cases from Italy, France, United Kingdom, Poland and Germany (2000-2009), confirmed the rarity of this disease and critical role of surgical resection as a therapeutic and prognostic identifier [2]. Despite its rarity, pancreatoblastoma is considered the most common malignant pediatric pancreatic tumor. Most occur in the 1st decade of life, with a mean of 2.4 years of age. In the majority it presents as an incidental abdominal mass [3].

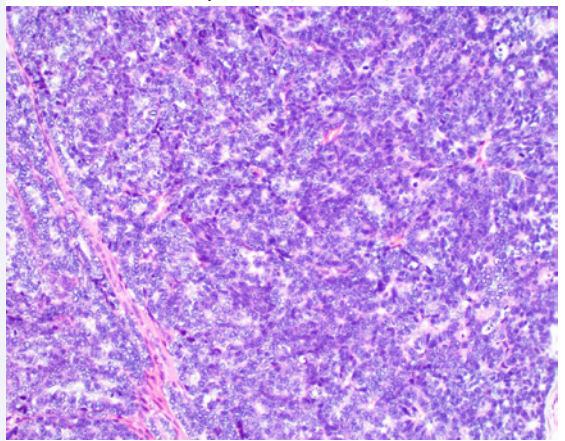
Pancreatoblastomas occur with equal frequency in the head and tail of the pancreas. Grossly the tumors appear partially circumscribed with prominent lobulation. Microscopically, the tumor shows both epithelial and stromal components. Mild nuclear pleomorphism can be seen and foci of necrosis are commonly identified (Figures 1A-1C). The epithelial components can show an acinar, solid or squamoid corpuscle formation. Squamoid corpuscle, especially, is considered to be a hallmark of pancreatoblastoma (Figure 2A-2B). Stromal components vary from paucicellular bands to hypercellular foci consisting of plump fibroblasts, commonly identified in infants [3].



Pancreatoblastoma with lobular growth pattern with stromal bands (1A, H&E, 4x)



Areas of necrosis are commonly identified (1B, H&E, 10x)



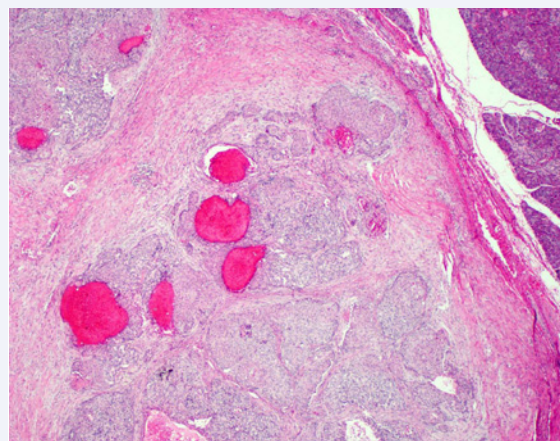
Higher power shows the acinar and solid growth patterns (1C, H&E, 20x)

Figure 1 Pancreatoblastoma with lobular growth pattern with stromal bands (A, H&E, 4x). Areas of necrosis are commonly identified (B, H&E, 10x). Higher power shows the acinar and solid growth patterns (C, H&E, 20x).

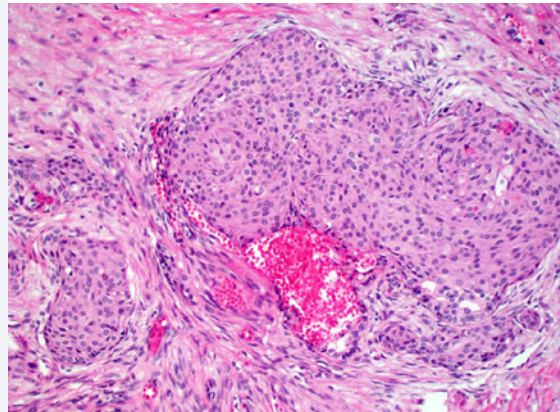
With immunohistochemistry, the tumor shows evidence of acinar differentiation, with positivity for trypsin, chymotrypsin or lipase. Stains for endocrine differentiation, synaptophysin, chromogranin, and neuron-specific enolase are often positive. Nuclear and cytoplasmic beta-catenin expression is reported, especially in the squamoid corpuscles in 80% of cases [4,5].

While the molecular genetics of pancreaticoblastoma are not

entirely understood, a number of studies have found alterations of Wnt pathway and allelic loss on 11p loci common in pancreaticoblastoma [5-7]. Abraham et al, found APC/beta-catenin pathway aberrations in 67% and an allelic loss on chromosome 11p in 86% of cases [5]. Kerr et al also demonstrated maternal allele LOH in the 11p15.5 region and increased expression of IGF2 expression [6]. The same locus is also found affected in children with Beckwith-Wiedemann syndrome (BWS). BWS is a maldevelopmental syndrome characterized by tissue overgrowth, organomegaly and an increased risk for embryonal tumors including pancreaticoblastoma, Wilms' tumor, hepatoblastoma, and rhabdomyosarcoma [8]. Abraham et al reported a case of pancreaticoblastoma in a patient with familial adenomatous polyposis with germline mutation and biallelic inactivation of APC in the patient's tumor. These authors report somatic alteration of APC/beta-catenin pathway and/or nuclear accumulation of beta-catenin protein in the majority of cases studied. As aberrations of this pathway are also common to hepatoblastomas, a similar genetic basis between them is suggested [5]. Jiao et al by performing whole-exome sequencing on pancreatic tumors with acinar differentiation (including two cases of pancreaticoblastoma) demonstrated mutations in SMAD4 and somatic mutations in CTNNB1 [9].



An additional case of pancreaticoblastoma with a lobular growth pattern and stromal bands, as well as squamous morules notable at low power (arrow) (2A, H&E, 4x)



Squamous morules (2B, H&E, 20x)

Figure 2 A second case of pancreaticoblastoma with a lobular growth. Squamous morules are present at low power (A H&E, 4x). Squamous morules (B, H&E, 20x). Higher power image of squamous morule with alpha-1 antitrypsin inclusions.

The behavior of pancreatoblastoma is that of a malignant neoplasm with recurrence and metastasis. However, it is a potentially curable malignancy, with an initial complete resection correlating with long-term survival [3]. The tumor is treated with surgical resection for both the primary and metastatic tumor. To optimize the chances of a complete resection in high-stage tumors, the EXPERT group recommends neoadjuvant chemotherapy. Pancreatoblastoma is generally considered a chemosensitive tumor. However, a standard regimen has yet to be defined; some follow a regimen usually adopted for hepatoblastoma, due to the similarities between these tumors [2].

SOLID PSEUDOPAPILLARY NEOPLASM OF THE PANCREAS

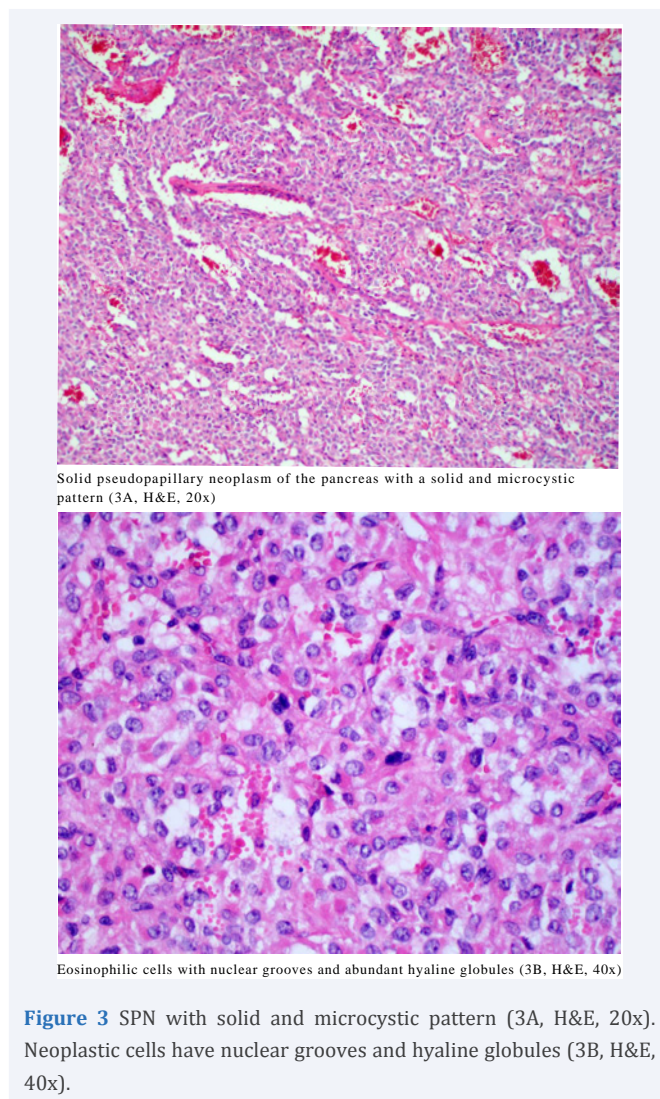
Solid pseudopapillary neoplasms (SPN) occur most classically in young female patients (mean age of 22 years) and are well reported in children and adolescents. It generally behaves as a low grade neoplasm with a good prognosis, though aggressive behavior has been reported. Some studies suggest a lower female predominance of SPN in children, with male-to-female ratios that can approach 1:1.75, instead of the 1:9.78 reported for all age groups [10]. Children with SPN often present differently than adult patients. Lee SE et al compared the clinical features of adults and children with SPN. In the adult group, the diagnosis was usually made incidentally during screening with detection of a mass. By contrast, all of the children were symptomatic. The mean diameter of the tumors based on pathological examination was 6.0 cm (range, 1.5-14 cm) in adults and 8.0 cm (range, 3.5-14 cm) in children. In adults, the pancreatic body or tail was the most common location of the tumor. However, in children, the pancreatic head was the most common site [11].

The cellular origin of SPN has not been fully determined and studies have suggested both exocrine, neuroendocrine, along with centroacinar cells [12]. The gross appearance of SPN includes a well circumscribed encapsulated cystic mass, which may be hemorrhagic and necrotic. Histologically, SPN is a cellular neoplasm with cells often in several layers around fibrovascular stalks, appearing papillary in nature. A predominantly solid or microcystic pattern is also identified (Figure 3A). SPN is composed of loosely-cohesive uniform cells with grooved nuclei and eosinophilic or clear cytoplasm. Intracytoplasmic PAS+ hyaline globules may also be found (Figure 3B).

SPN characteristically shows an abnormal staining pattern with nuclear and cytoplasmic positivity for β -catenin, in parallel with activating mutations in β -catenin exon-3 gene [13]. SPN also characteristically demonstrates positivity for progesterone receptor, α -1 antitrypsin receptor, neuron specific enolase and CD10 by immunohistochemistry [10].

Investigators have demonstrated a loss of heterozygosity at 5q22.1 in a subset of SPN [13]. As in pancreatoblastoma, a genetic alteration leads to an abnormality of the Wnt signaling pathway [14,15]. A study by Wu et al, utilizing whole-exome genomic sequencing, most notable finding in their assessment of SPNs was the paucity of genetic alterations. While all tumors contained mutations of CTNNB1, only one of the eight tumors exhibited any LOH [16].

Surgical resection is the treatment of choice for SPN, with the procedural type based on the location of the mass. Complete



resection with negative margins typically proves curative. Despite large tumor size and ability to extend locally, children and adolescents with SPN do very well with surgical resection [17]. Predicting aggressive behavior is difficult and investigators have varied in defining the clinically relevant criteria [10].

PANCREATIC ENDOCRINE NEOPLASMS

Pancreatic endocrine neoplasms (PEN) are not rare; although in comparison to the adult population, their incidence in children is much lower. PEN comprises one of the common pediatric tumors of the pancreas. A study from Boston Children's Hospital, by review of pancreatic neoplasms over a 90-year period (1918-2007), report neuroendocrine neoplasms as the most common subtype, with 5 of the total 18 cases identified [18]. Pancreatic endocrine neoplasms can be sporadic or associated with genetic syndromes including MEN1, Von Hippel-Lindau, neurofibromatosis, and tuberous sclerosis [19]. Of symptomatic insulinomas diagnosed during a 60-year period at the Mayo clinic, 4.9% occurred in children over 10 years of age [20]. Endocrine tumors may or may not be capable of producing a hormonally active peptide product. If they are, the peptide production may manifest as a clinical syndrome, and islet tumors

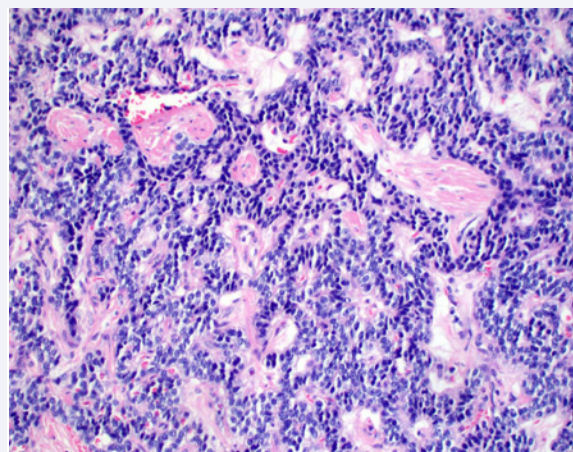
will be designated as functioning. In children, the most common type of functioning endocrine tumors is the insulinoma followed by gastrinoma. Other types of functioning and nonfunctioning pancreatic endocrine tumors are exceedingly rare or have never been reported in children [21].

Insulinomas can lead to hyperinsulinemic hypoglycemia. Most patients present with the Whipple triad of fasting hypoglycemia, symptoms of hypoglycemia and immediate resolution of symptoms with intravenous administration of glucose. In children especially, it can cause significant neurological defects with seizures and coma [22]. When hypoglycemia occurs in children, an insulinoma must be considered and imaging work-up performed. Gastrinomas are the second most common in children, occurring in 40% of individuals with MEN1 [23]. Gastrinomas cause the Zollinger-Ellison syndrome. Patients frequently have multiple or recurrent peptic ulcers in uncommon locations. Gastroesophageal reflux, heartburn and hypersecretory diarrhea are also common symptoms [21].

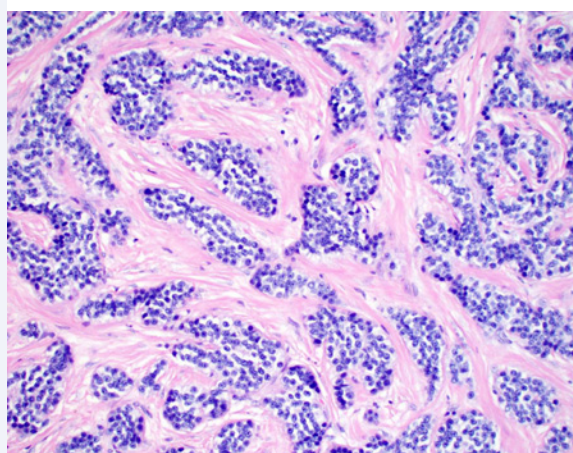
Grossly, most pancreatic endocrine neoplasms are well-circumscribed and homogenous. Histologically, the tumors are composed of round and uniform cells with a salt and pepper chromatin. The cells can form a nesting, trabecular, gyriform or rosette-like pattern. Often several of these patterns will be identified within different regions of the tumor [24]. (Figures 4A and 4B). Necrosis is uncommon. The finding of amyloid is highly suggestive of an insulinoma [21]. Immunohistochemistry is positive for neuroendocrine markers including synaptophysin and chromogranin (Figure 4C).

The prognosis of pancreatic endocrine neoplasms depends on factors including size at diagnosis and status as localized or metastatic at presentation. Prediction of biologic behavior based on histologic criteria is difficult [25]. Insulinomas are typically solitary (except in MEN1), small (less than 2 cm) and benign. Malignant insulinomas are rare in children. Gastrinomas typically show a higher risk of malignant behavior, with the rate of tumor related death less in MEN 1 than in sporadic cases [25].

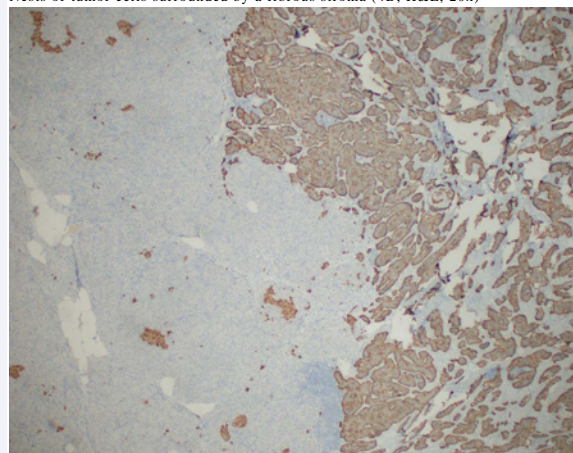
Exomic sequences of sixty-eight neuroendocrine tumors performed by Jiao et al. showed that the most frequent mutated genes were those involved in chromatin remodeling: 44% of the tumors had somatic inactivating mutations in MEN-1 (which encodes menin, a component of a histone methyltransferase complex), and 43% had mutations in genes encoding either of the two subunits of a transcription/chromatin remodeling complex consisting of DAXX (death-domain associated protein) and ATRX (alpha thalassemia/ mental retardation syndrome X-linked) [26]. Clinically, mutations in the MEN1 and DAXX/ATRX genes were associated with better prognosis. They also found mutations in genes in the mTOR (mammalian target of rapamycin) pathway in 14% of the tumors. Immunotherapy targeting the mTOR pathway may provide additional effective therapy in patients who harbor these mutations; especially in NET's not amenable to surgical resection [26]. mTOR, a serine/threonine kinase, plays a crucial role in transducing multiple signals mediated by the phosphatidylinositol 3 kinase (PI3 K)/protein kinase B (AKT) pathway. It is believed that aberrant activation of this pathway at the beginning of neuroendocrine carcinogenesis could result in a loss of tumor suppressor genes' function or loss of the function of TSC-1/TSC-2 complex [27].



Pancreatic endocrine neoplasm with rosette forming and trabecular patterns (4A, H&E, 20x)



Nests of tumor cells surrounded by a fibrous stroma (4B, H&E, 20x)



Chromogranin stain highlighting tumor cells (4C, immunostain, 4x)

Figure 4 PEN with trabecular and rosetting growth (4A. H&E, 20x). Tumor nests and intervening fibrous stroma (4B, H&E, 20x). PEN with diffuse positivity for chromogranin (4C, IPEX, 4x).

As with the other pancreatic neoplasms presented, optimal treatment of NET's relies primarily on a complete surgical excision. Surgical resection of both primary and metastatic disease has been associated with a better prognosis. Molecular based targeted therapies for neuroendocrine neoplasms have shown promise. In addition to mTOR, somatostatin therapies

have been used to control the early symptoms of NET's and decreased the time to disease progression [27]. Somatostatin receptors induce expression of the pro-apoptotic proteins p53 and Bax and inhibit pathways involved in proliferation. Therapies targeting pro-angiogenic molecules such as VEGF have also shown promise, with clinical trials indicating an increase in progression free survival by addition of sunitinib, a broad-spectrum tyrosine kinase inhibitor targeting VEGF, to the therapeutic regimen [27].

In summary, the pediatric pancreatic neoplasms presented here are rare with morphologic features which can overlap with each other and/or with metastatic entities. Due to their rarity, our understanding of biological behavior and treatment of the lesions in children has been limited. With greater knowledge of their syndromic associations and/or cellular origin, we can better categorize and treat these entities.

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