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Neuroendocrine tumor of the pancreas causing biliary obstruction in a 12 year-old girl: A case report and literature review☆

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ABSTRACT

Pancreatic tumors are uncommon in children and rarely result in biliary obstruction. A previously well 12-year old female presented with a one-week history of fatigue, pruritis, and painless jaundice. Abdominal ultrasound demonstrated a mass in the pancreatic head associated with dilation of the common bile duct. Further workup included abdominal MRI, CT and endoscopic retrograde pancreaticogram (ERCP) with biliary stenting. Octreotide scan did not reveal uptake in the pancreatic tumor. Percutaneous biopsies were consistent with a grade 2 pancreatic neuroendocrine tumor (NET). Preoperative imaging demonstrated involvement of the portal vein. The patient was brought the operating room for a pancreaticoduodenectomy and portal vein resection. Final pathology revealed a T3N1M0 pancreatic NET. The patient recovered uneventfully.

Pancreatic tumors are exceedingly rare in children and adolescents. Neuroendocrine tumors (NET) account for approximately 25% of pediatric pancreatic masses [1,2]. NET arise from endocrine tissues of the pancreas and are classified as either non-functioning or functioning. Functioning NETs secrete various peptide hormones, which act at distant sites and can result in a variety of clinical syndromes. Pancreatic NETs can be benign or malignant, however the majority of non-functioning tumors are malignant. Pancreatic tumors in children rarely present with biliary obstruction, owing to the expansive rather than infiltrative growth patterns of the common pediatric pancreatic neoplasms [3,4].

1. Case report

A 12 year-old female was referred to our center after presenting to her local emergency department with a one-week history of fatigue, pruritis, and acholic stools. She was visibly jaundiced. An abdominal ultrasound at her local hospital suggested a mass within the head of the pancreas. Her laboratory tests were: total bilirubin 136 umol/L, direct bilirubin 84.6 umol/L, alkaline phosphatase 543 U/L, alanine aminotransferase 172 U/L, and aspartate aminotransferase 75 U/L. Serum lipase was within normal limits. Following these investigations, the patient was transferred to our institution for further workup in hospital.

Magnetic resonance imaging (MRI) of the abdomen demonstrated extensive dilation throughout the intra and extrahepatic biliary tree (Fig. 1). The common bile duct (CBD) measured 2.5 cm with an abrupt transition at the pancreatic head. Within the pancreatic head there was a 3 cm solid, smoothly marginated mass. Computed tomography (CT) of the abdomen (Fig. 2) was also performed to better assess the surrounding vasculature. The lesion was found to be in direct contact with the portal vein (PV) with a narrowed segment, suspicious for tumor infiltration. Both the superior mesenteric artery (SMA) and superior mesenteric vein (SMV) appeared to be uninvolved. There also appeared to be 5 × 3 mm calculus within the CBD. Because of the biliary obstruction and possible CBD stone, the patient underwent endoscopic retrograde pancreaticochoangiogram (ERCP). This identified a tight stricture, 1 cm from the ampulla, for a distance of 5 mm. No stone was identified and a plastic stent was placed for biliary drainage. ERCP

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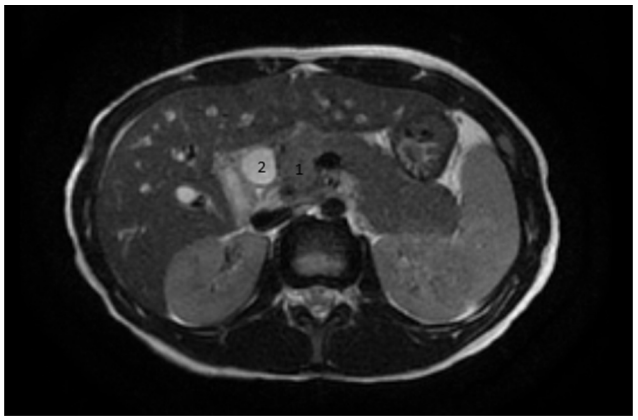

Fig. 1. T2-weighted magnetic resonance imaging (MRI) demonstrating a mass in head of pancreas (1) causing massive dilatation of the common bile duct (2).

was arranged prior to obtaining a tissue diagnosis because the patient was highly symptomatic with pruritis.

Tumor markers were sent in an attempt to determine the etiology of this mass. Serum carbohydrate antigen 19-9 (CA19-9) was mildly elevated at 38 U/ml. Serum carbohydrate antigen 125 (CA-125), β-human chorionic gonadotropin (β-HCG), alpha-fetoprotein (AFP) and Immunoglobulin 4 (IgG4) levels were within normal limits. Furthermore, serum gastrin, insulin and chromogranin A were also non-elevated. Twenty-four hour urine collection revealed normal levels of vanillylmandelic acid (VMA), homovanillic acid (HVA), and 5-hydroxyindole acetic acid (5-HIAA). A bone marrow aspirate was also normal, making the diagnosis of leukemia unlikely. CT chest was also normal.

This patient's case was then reviewed in multi-disciplinary tumor board rounds with radiology, pediatric medical oncology, pathology, and pediatric surgery. A joint decision was made to proceed with a surgical biopsy, as the group felt that percutaneous biopsies were less likely to result in adequate tissue for pathologic interpretation and had a theoretical potential for seeding the tumor through the needle tract. She was brought to the operating room for laparoscopic biopsies of the pancreatic head. Tissue samples sent to pathology for frozen sections revealed only normal pancreatic tissue. As a result, interventional radiology was consulted to perform ultrasound-guided, percutaneous biopsies while the patient was under the same general anesthetic. These specimens demonstrated a grade 2 NET (2 mitoses per 10 high power fields, Ki-67 index 12%). Unfortunately, the patient bled post-biopsy and underwent angiographic embolization of

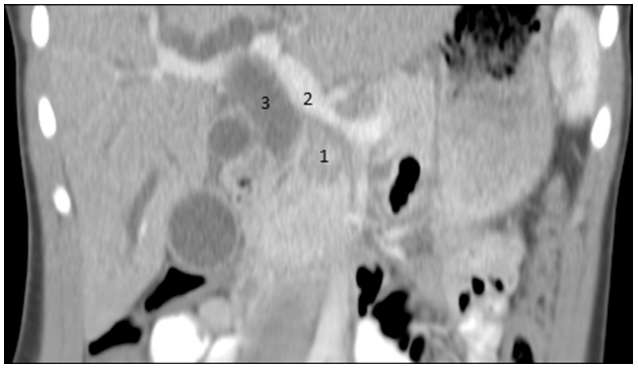

Fig. 2. Coronal slice from computed tomography (CT) scan of the abdomen: pancreatic mass (1), portal vein (2), and dilated common bile duct (3).

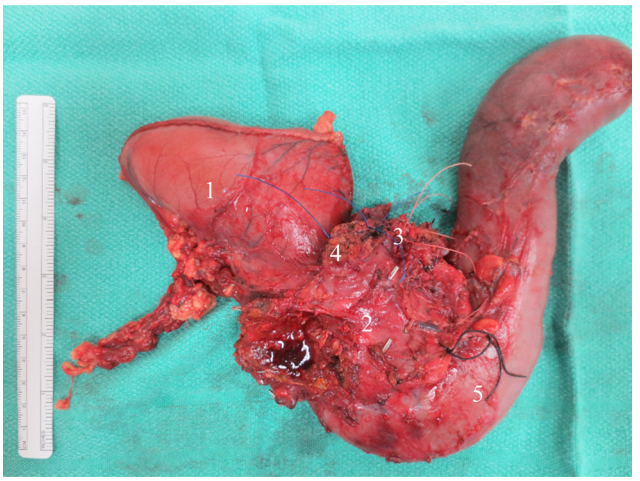

Fig. 3. Posterior view of specimen: gastric antrum (1), pancreatic tumor (2), bile duct (3), pancreatic neck margin (4), and duodenum (5).

branches of the pancreaticoduodenal artery. She tolerated this well and eventually recovered.

An octreotide scintigraphic scan was then performed. This revealed no significant octreotide uptake within the known pancreatic tumor, and no evidence of octreotide-positive metastatic disease. Although not available in our center, but commonly utilized in Europe, a 68Ga DOTATOC/68Ga DOTATATE PET scan would have been a good alternative imaging test for preoperative evaluation. If positive, this would have provided an imaging modality for postoperative surveillance.

The patient was then reviewed in multi-disciplinary neuroendocrine tumor board rounds. In conjunction with our adult hepatopancreaticobiliary surgeons, a decision was made to take the patient to the operating room for a pancreaticoduodenectomy (Whipple's procedure) with a plan for possible PV resection. The mass was visible in the pancreatic head, with firm nodes along the uncinate margin. The nodal tissue along the hepatic artery and posterior to the SMA was cleared and sent with the specimen. She underwent a standard pancreaticoduodenectomy with an end-to-side pancreaticojejunostomy, end-to-side hepaticojejunostomy, and a loop gastrojejunostomy. A frozen section of the pancreatic resection margin was sent to pathology before reconstruction, which was negative for malignancy (Fig. 3). A short segment (5 mm) of the PV was resected, due to significant tumor adherence, and reconstructed using an end-to-end anastomosis (Fig. 4). Total clamp time was 25 min. We elected to perform a primary anastamosis of the PV rather than a vein graft due to the short segment of resection, and the fact that it came together under no tension. On final pathology the PV was not infiltrated with tumor and therefore the dense adherence was likely desmoplastic reaction.

Final pathology demonstrated a T3N1M0 grade 2 (World Health Organization Classification) pancreatic NET with negative resection margins. The tumor extended beyond the pancreas but did not involve the celiac axis or SMA. Lymphovascular and perineural invasion were present. The Ki-67 index ranged from 3% to 20%. Five out of nineteen lymph nodes were positive. She was again presented at our neuroendocrine tumor board. Given her complete resection and the non-functionality of her tumor, no further treatment was recommended. Adjuvant treatment of completely resected (R0) pancreatic neuroendocrine tumors is somewhat controversial, however after consultation with international experts and a through literature review, it was felt that the potential

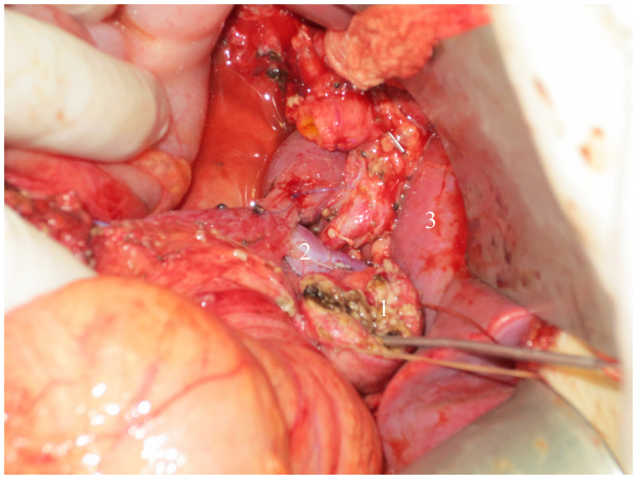

Fig. 4. Following removal of specimen: probe marking pancreatic duct (1), superior mesenteric vein (2), and liver (3).

for toxicity in a young patient outweighed the questionable benefit. She will require pancreatic imaging every 3 months for the next 2 years and continued long-term follow-up. Genetic screening for multiple endocrine neoplasia (MEN) and Von Hippel-Lindau (VHL) syndromes has been undertaken given the rarity of pancreatic NET and the implication on further screening.

The patient recovered uneventfully post-operatively. An asymptomatic portal vein thrombus was demonstrated on screening ultrasound and anti-coagulation was initiated. The etiology of this thrombus was felt to be secondary to endothelial trauma from the reconstruction. At 6 weeks, the PV thrombosis had completely resolved and anti-coagulation was discontinued. At her 3-month follow-up, she continued to do well with no signs of recurrence on CT.

2. Discussion

Pancreatic tumors in children and adolescents are exceedingly rare, and as such, there is a paucity of data on this topic. The literature consists predominately of single institution case series carried out over long time periods. Investigators from Memorial Sloan-Kettering published a retrospective review of pediatric patients less than 21 years of age with malignant pancreatic tumors [3]. Patients with MEN were excluded. They identified sixteen patients with pancreatic neoplasms over a 35-year time period. Solid pseudopapillary tumors (SPT) were the most common pathological subtype, followed closely by pancreatoblastomas (PB) [3]. Only 2 patients (12.5%) had NETs: one was non-functional and the other was a malignant vasoactive intestinal peptide-secreting neuroendocrine tumor (VIPoma). The largest case series published to date is from the Hospital for Sick Children in Toronto, Canada. In this series 27 patients were identified over a 34-year time period (1986–2010). Again, SPT was the most common pathology (66.7%) followed by NET (22.2%). There were no patients with PB in this series [5]. Half of NETs were functional (2 insulinomas, 1 glucogonoma) [5]. Preoperative biopsy was only performed in a third of cases, however 80% of biopsies were diagnostic, and no morbidity was attributed to biopsy [5].

Other reports of pancreatic masses in children include: ductal adenocarcinoma, acinar cell carcinoma, peripheral neuroectodermal tumor (PNET), rhabdomyosarcoma, fibrosarcoma, Ewing sarcoma, lymphoma and teratoma [3,5–7]. Ductal adenocarcinoma, the predominant tumor type in adults, is exceptionally rare in the pediatric population. Non-neoplastic etiologies such as autoimmune pancreatitis are also possible [4].

The majority of children or adolescents with pancreatic neoplasms present with abdominal pain, emesis or a palpable mass [3,5]. Biliary obstruction is rare [3,4]. Unlike ductal adenocarcinoma, the majority of pediatric pancreatic tumors exhibit an expansive growth pattern, and push nearby structures aside rather than invading them. Furthermore, they do not have a predilection for the pancreatic head, with only 38% found in this location in the series from Memorial Sloan-Kettering [3]. In particular, NET have a predilection for the pancreatic tail [5].

Complete surgical resection is the mainstay of treatment for malignant tumors of the pancreas in children. Due to the infrequent nature of these neoplasms and the histologic heterogeneity, the role of chemotherapy and radiotherapy is anecdotal, and their role in the adjuvant setting has yet to be clearly established [1,3]. In contrast to the adult population, most children have resectable disease at the time of presentation [3]. In a single-center retrospective review of pediatric patients undergoing pancreatic resection for mass lesions, 19 of 20 had an R0 resection [1]. There was no peri-operative mortality, but 25% of patients experienced peri-operative morbidity. The most common complication was a pancreatic leak (15%) [1]. Median follow-up was 49.5 months and no patients experienced recurrence. Four patients (20%) developed pancreatic exocrine deficiency and one (5%) became diabetic postoperatively. These results are similar to those reported from Memorial Sloan-Kettering and MD Anderson [1,3,8].

Extra-appendiceal NETs are rare in children, with an incidence of 0.5 per million [9]. Approximately 25% of pediatric pancreatic neoplasms are NETs [1,2,5]. The WHO grading system for NET depends entirely on histopathologic criteria, including proliferation index (Ki-67 index), mitotic count, and the presence or absence of tumor necrosis. The most common symptom at diagnosis is abdominal pain (85%) and weight loss (46%), while jaundice is rare [9]. The majority of pancreatic NETs in children and adolescents are non-functioning tumors [9]. In some case series, up to 50% of children had metastatic disease at presentation, and localized disease is less common in pancreatic NET than with other sites of extra-appendiceal NET [8,9]. These tumors may be associated with genetic syndromes such as MEN, Von Hippel-Lindau syndrome, Neurofibromatosis type 1, or tuberous sclerosis [5,8]. It is unknown whether high-grade tumors (WHO grade 2 or 3) are more common in the pediatric population.

The gold standard of treatment for extra-appendiceal NET is complete surgical resection. If complete surgical resection is not achieved, these tumors have a tendency to recur locally or metastasize [8]. NETs respond poorly to chemotherapy. Over-expression of the somatostatin receptor is common in these tumors, so peptide receptor radionucleotide therapy is possible [8]. There is no standardized chemotherapy regimen in children, but in adults, both streptozotocin and fluorouracil are first-line treatments for stage III or greater [9]. Chemotherapy may have many adverse effects on the developing child, including failure to thrive, infertility and a significant risk of secondary malignancy. The case series from MD Anderson estimated a 3-year overall survival rate for children with pancreatic NET of 75% (95% CI 13%–96%) [8].

3. Conclusions

Pancreatic tumors in children and adolescents are rare. Pancreatic NETs only represent 25% of these neoplasms. Unlike adults, these tumors rarely present with biliary obstruction and have a good prognosis if complete surgical resection can be achieved. The preoperative work-up of a child with a pancreatic mass should include IgG4 levels as well as tumor markers (AFP, CA19-9, chromogranin A). Core biopsies should be strongly considered to avoid unnecessary surgical management in patients with

autoimmune pancreatitis or lymphoma. Overall survival is significantly better among children with localized disease compared to those with distant spread.

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