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Acinar cell carcinoma in childhood: A case report of a very rare tumor

Research Article

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Abstract: **Introduction:** Pancreatic tumors are reported rarely in childhood and represent an extremely rare entity in Pediatric Oncology. One of the least common types of pediatric pancreatic tumor is acinar cell carcinoma (ACC). We aim to present a rare case of ACC and the difficulties we faced during diagnosis and treatment.

Patient and Methods: An 8-year old girl presented with jaundice. Workup revealed a tumor originating from the head of the pancreas with multiple metastatic lesions in her liver. Evaluation of tumor markers revealed elevated levels of AFP. Pathology report was indicative of acinar cell carcinoma of the pancreas.

Results: After consulting the EXPeRT group (European Cooperative Study Group for Pediatric Rare Tumors), chemotherapy was initiated. Partial response was observed after the first 4 courses with decrease of AFP levels. While planning her surgery, AFP elevated and a second-line course of chemotherapy was administered. Our patient underwent Whipple's Duodenopancreatectomy with partial metastasectomy. Although the postoperative period was uneventful, AFP continued to rise even after postoperative chemotherapy was administered. There were signs of metastatic disease progression. Our patient received a third-line regimen with no improvement. She received local radiotherapy and a next-line chemotherapy course. Local relapse and metastatic disease progression placed our patient in palliative care. She passed away nine months after the initial diagnosis.

Conclusions: Acinar cell carcinoma of the pancreas is a rare type of pediatric cancer with very challenging diagnosis and treatment. Cooperation at the European level and multicenter management of those rare cases is vital for the optimum outcome.

Keywords: *Pancreatic cancer • children • acinar cell carcinoma • childhood pancreatic cancer*

1. Introduction

Pancreatic tumors are reported rarely in childhood, and thus, represent an extremely rare entity in Pediatric Oncology. As a result, the published literature is limited and mainly based on small series and case reports. A recent report estimates that the incidence for pediatric pancreatic cancer was 0.018 newly diagnosed cases per 100000 people.[1] In a recent systematic review, solid pseudopapillary tumor is considered the most prevalent histological type among children with pancreatic cancer, followed by pancreatoblastoma,[2] whereas exocrine carcinomas, such as ductal adeno-carcinomas (DCA) and acinar cell carcinomas (ACC), occur less often. As a rare entity, difficulties occur during the diagnosis and treatment of those tumors. We intend to present a

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rare case of acinar cell carcinoma of the pancreas in a child that was diagnosed in our center, as well as the difficulties we faced during the diagnosis and treatment.

2. Materials - Methods

We present a case of an 8-year old girl who was diagnosed with pancreatic tumor. She was admitted to our hospital with jaundice. She presented with paler feces and darker urine, which had initiated fifteen days prior to her admission. She did not experience any abdominal pain but she developed anorexia. No fever or weight loss was reported. The physical examination revealed a palpable mass in her upper abdomen. Her complete blood count test was within normal range (WBC: 6500/μl, Neut: 49.7%, Lymph: 39.8%; Hb: 13.0 g/dl, Hct: 37%, PLT: 332000/μl). Blood chemistry revealed elevated hepatic enzymes SGOT: 123 U/l (normal values = 8–48 U/l) – SGPT: 268 U/l (normal values = 7–55 U/l), significantly elevated γ-GT = 182 U/l (normal values = 8–61 U/l) and alkaline phosphatase (ALP): 549 U/l (normal values = 40–129 U/l) and conjugated hyperbilirubinemia with total bilirubin = 5.6 mg/dl (normal values = 0.2–1.2 mg/dl) and conjugated bilirubin = 4.5 mg/dl (normal values < 1.0 mg/dl). LDH, amylase, lipase and uric acid were within normal range.

The initial U/S and CT scan revealed a 5.0 X 4.7 X 3.6 cm tumor probably originating from the head of the pancreas. In the center of this tumor, areas of calcification were detected. The tumor caused dilation of the common bile duct (maximum diameter = 1 cm – normal value < 0.7 cm) and intrahepatic bile ducts. A mild dilation of the main pancreatic duct was also present. The tumor displaced the nearby vessels and caused thrombosis (2 cm) in the portal vein shortly before the hepatic hilum. None of the nearby lymph nodes exceeded a diameter of 6 mm. Chest CT scan was negative for metastatic lesions but MRI of the abdomen revealed multiple (more than 40) metastatic lesions in her liver (maximum diameter = 1.2 cm).

Evaluation of tumor markers revealed an elevated AFP = 1870 ng/ml (normal value < 10 ng/ml). CEA, Ca 125 and Ca 19.9 were within normal range.

A CT guided fine needle biopsy of the tumor was performed. The pathology report was indicative of a hepatoid pancreatic neoplasm compatible with an acinar cell carcinoma of the pancreas. Histologically, it was an epithelial tumor of pancreas with acinar differentiation exhibiting a solid growth pattern with sheets and nests of polygonal cells with moderate amounts of granular eosinophilic or amphophilic cytoplasm centrally located nuclei and prominent nucleoli. Squamoid nests, the histologic hallmark of a pancreatoblastoma, had not been observed. Immunohistochemically, the tumor cells showed strong positivity for Hep-Par-1, CD 10[canalicular], a-Fpr, CK18, CK8/18 and CK7 abs.

In order to proceed with her treatment, we received the experienced guidance of EXPeRT group (European Cooperative Study Group for Pediatric Rare Tumors), which provided the help we needed to diagnose and treat a very rare tumor.

She required Percutaneous Biliary Drainage (PBD) via a Percutaneous Transhepatic Cholangiography (PTC) catheter to minimize her bilirubin rates in order to initiate chemotherapy. Her pre-chemotherapy AFP was 3719 ng/ml.

3. Results

She initiated chemotherapy according to “EXPeRT Consensus Recommendations for Pancreatoblastoma – version 2.2” with a course of PLADO (cisplatin 80 mg/m^2 d1 – doxorubicin 30 mg/m^2 d2-3). Although elevated at first (7471 ng/ml), AFP rate decreased before her second course (2610 ng/ml). Abdomen U/S revealed regression in primary tumor. AFP kept decreasing in the following weeks, to a minimum value of 879 ng/ml. Our patient received 4 courses of PLADO in total. The new MRI scan revealed a further decrease in primary tumor size (2.9 X 2.2 X 1.9 cm) and a decline in the number and size of her hepatic metastases (maximum diameter = 0.6 cm). While planning her surgery, her AFP value began to rise (1951 ng/ml). As a result, she received a course of FOLFOX (5-FU 1000 mg/m^2 d1-2 – Leucovorin 400 mg/m^2 d1 - Oxaliplatin 85 mg/m^2 d1) before her planned surgery.

Our patient was referred to Birmingham’s Paediatric Liver Unit Team and a decision was taken to offer a Whipple operation with portal vein resection and reconstruction. Furthermore, the plan was to complete a right hepatectomy and non-anatomical resection of the left lobe lesions. She underwent a Whipple’s Duodenopancreatectomy with portal vein/superior mesenteric vein thrombectomy, cadaveric O->B interposition vein graft and non-anatomical resection of Segment 3 lesion four months after her initial diagnosis. The planned right hepatectomy and non-anatomical resection of the left lobe lesions was not performed due to instability during the surgery.

The histological report revealed acinar cell carcinoma of the head of the pancreas. The greatest tumor diameter was 4 cm (pT2). However, the resection was incomplete with positive pancreatic margins. There was no vessel or vein involvement. The hepatic artery

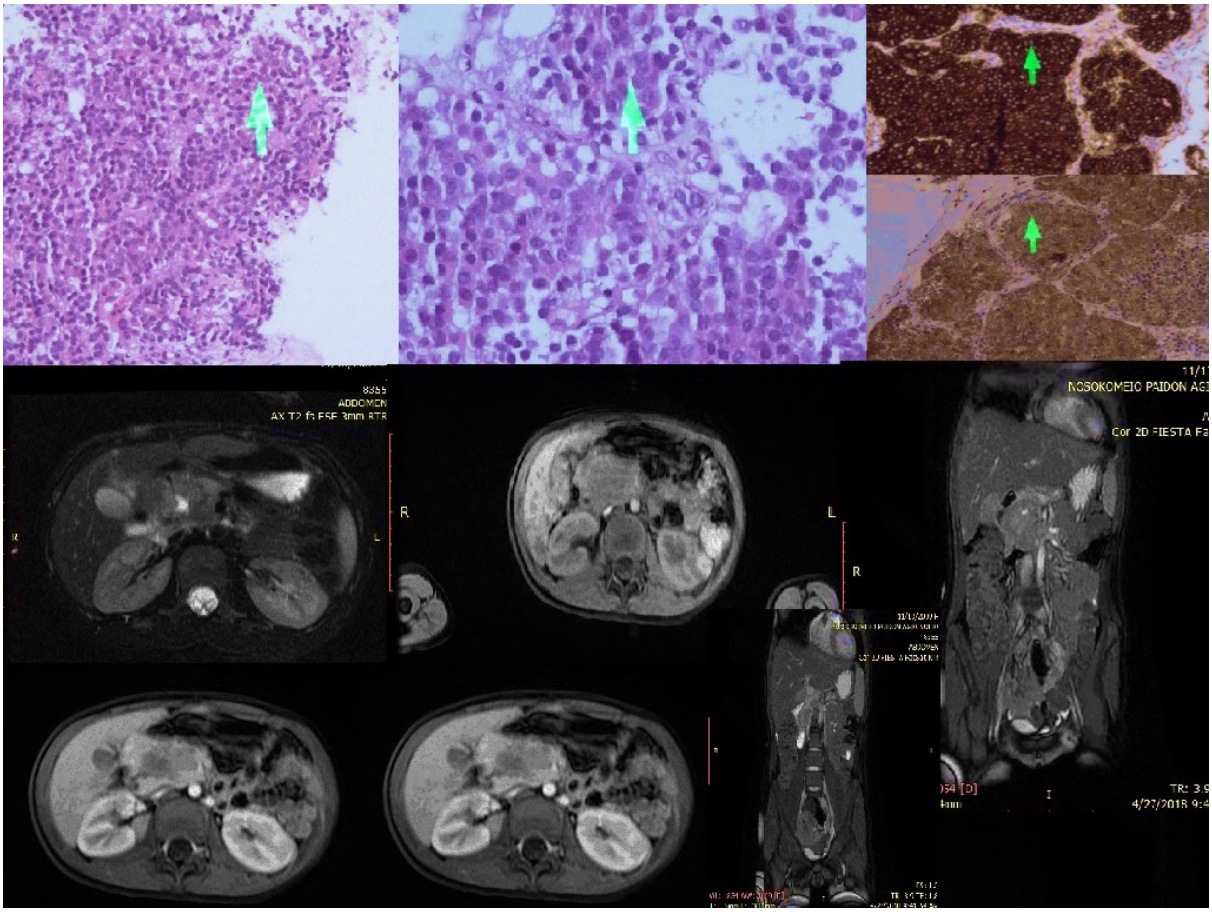

Figure 1: Histological samples and MRI scan of our patient.

lymph node was negative for disease, as well as the lymph node next to common bile duct. Direct invasion of intrapancreatic lymph node was reported (2/2). Metastasectomy revealed active disease in her liver. Her pre-discharge AFP value was 3905 ng/ml.

She returned to our center two weeks after the surgery. She had an uneventful postoperative period. However, AFP values continued to rise with a maximum value of 12225 ng/ml three weeks after the surgery. Therefore, we performed both chest and abdominal CT scan, which revealed no signs of lung metastasis or local relapse. Her hepatic metastatic disease seemed to worsen. She initiated chemotherapy with FOLFIRINOX (5-FU 1200 mg/m^2 d1-2 – Leucovorin 400 mg/m^2 d1 - Oxaliplatin 85 mg/m^2 d1 – Irinotecan 135 mg/m^2 d1). After the first cycle, abdominal MRI scan and ultrasound revealed an increase in her liver lesions' size and number with no signs of local relapse. Her AFP value was 17464 ng/ml. Three weeks after her previous chemotherapy course, she initiated a course of ICE (Ifosfamide 3000 mg/m^2 d1-3 – Carboplatin 600 mg/m^2 d3 –Etoposide 100 mg/m^2 d1-3). With the thought of urgent (living related) liver transplant, as the only chance to treat her, a PET/CT scan was performed, in order to verify the lack of local relapse. However, PET/CT scan revealed the hepatic metastases (SUVmax = 6.0) as well as para-aortic lymph nodes (SUVmax = 3.6) and lymph nodes posterior to the body of the pancreas (SUVmax = 2.4). Meanwhile, the girl developed severe abdominal pain. Abdominal ultrasound, abdominal MRI scan and MRCP confirmed the disease progression. During that time, her AFP value was 21712 ng/ml.

Our patient received palliative radiotherapy in tumor bed and liver (total dose: 24 cGy), without clinical improvement. Furthermore, she initiated palliative chemotherapy with gemcitabine (1000 mg/m^2 d1, 8, 15). She received 2 courses of gemcitabine before it was discontinued due to disease progression. Her last AFP value was 108877 ng/ml.

The girl was referred to the Pediatric Palliative Home Care Service of "MERIMNA". The interdisciplinary team, consisting of pediatricians, nurses, social worker

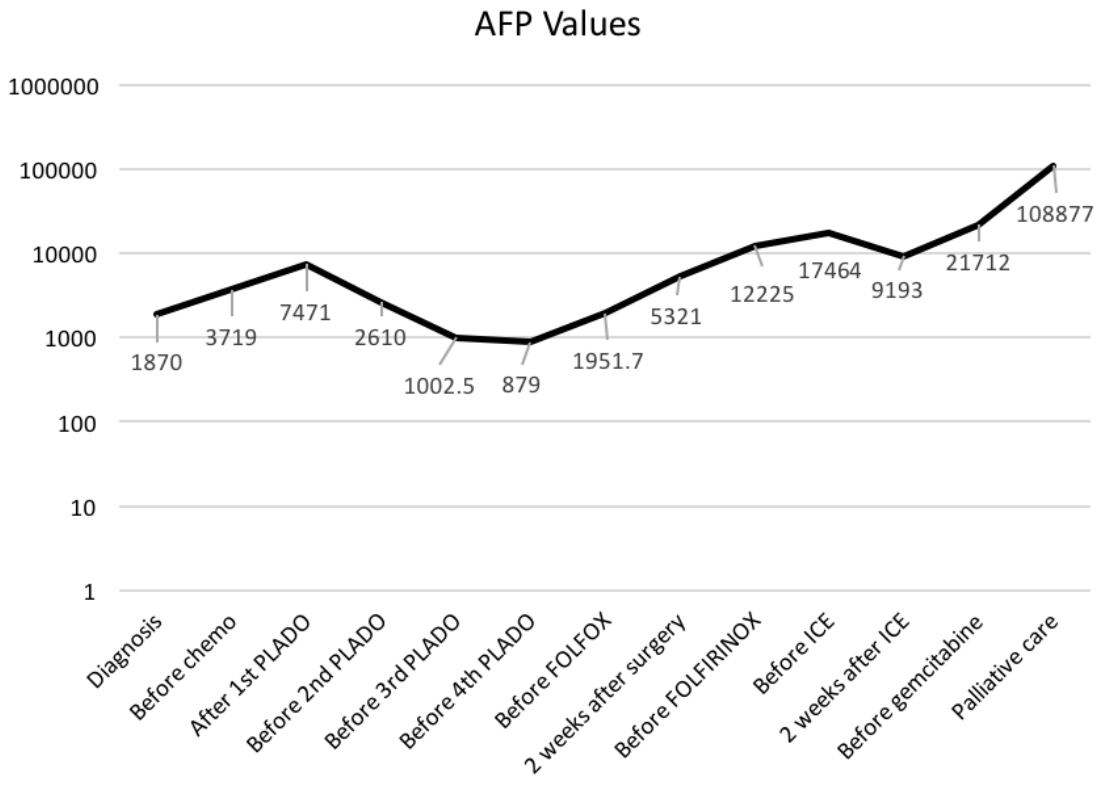

Figure 2: AFP values on major steps of our patient's treatment (ng/ml).

and psychologist, evaluated the physical symptoms and psychosocial needs of the girl and her family. In cooperation with them, the team designed an advanced care plan based on their needs and preferences. The main goal of the care at the final stage was the maintenance of a good quality of life. The symptoms that the team had to relieve included pain (somatic and psychological), anxiety, anorexia, dyspnea, illusions, delirium and urine retention. Psychosocial support was also offered to all members of the family (parents, siblings, grandparents). The girl passed away peacefully at her home, 9 months after her initial diagnosis, surrounded by her family, with the presence and support of the palliative care team's members. After the child's death, the pediatric palliative care team continued to support the family through bereavement care.

4. Discussion

As mentioned above, pancreatic neoplasms are extremely rare. Moreover, exocrine carcinomas occur less frequently. The most prevalent histological type of exocrine carcinomas in children is acinar cell carcinoma (ACC), while ductal adeno-carcinomas occurs more frequently in adults.[3] The number of cases reported in literature is extremely small. In the USA, there were 114 patients (< 16 years old) with pancreatic tumor registered in "The Surveillance, Epidemiology, and End Results (SEER)" database between 1973 and 2013, but only 6 cases of ACC.[4] In TREP (Tumori rari dell'età pediatrica) database, there were 21 patients with pancreatic tumor registered between 2000 and 2009, 2 of which had ACC.[5] In Germany, there were 55 patients (< 16 years old) with exocrine pancreatic tumor registered in German Pediatric Tumor Registry between 1980 and 2007. From those patients, only 5 had histological findings of ACC.[3] In the Memorial Sloan-Kettering Cancer Center (NY, USA), between 1967 and 2002, 17 cases of pancreatic neoplasms were diagnosed in children but only 1 case of ACC.[6] Generally, in literature, there are 29 cases of pediatric ACCs reported in 20 papers between 1970 and 2014. ACC is diagnosed more frequently in males (ratio male:female 18/11) with an average age of 9.57 years (range 3–16 years). Of those 29 cases, 14 carcinomas occurred in children > 10 years old.[7]

Most common site of pancreatic ACC is the tail of the pancreas, whereas our patient had a tumor originated from the head of the pancreas. The main clinical manifestation is abdominal pain and discomfort.

A palpable mass is usually reported. Nausea and vomiting is also a common manifestation of pancreatic ACC. Jaundice is an uncommon symptom of pancreatic ACC, but it was the main symptom in our patient. [7] Polyarthralgia, panniculitis and subcutaneous fat necrosis rarely occur in children with ACC. In contrast, they remain common symptoms of ACC in adults. The mechanism that develops those symptom is thought to be the lipase release by the tumor into the circulation.[8] Another common finding in ACC cases in children is the elevated level of AFP. AFP is reported elevated in all cases of ACC. A current hypothesis is that AFP production is related to acinar differentiation. [3,9] Cushing's syndrome occurs rarely in ACC cases, mainly due to ACTH production of the neoplastic cells.[10] Metastatic disease at the time of diagnosis is reported in as high as 41%, with half of those cases referring to regional metastases and the other half to distant metastases.[7]

Histological findings remain highly important in the differential diagnosis of ACC from other types of pancreatic neoplasms. Separating ACC from pancreatoblastoma and solid pseudopapillary tumor may prove a difficult task because of the overlapping features they present. Squamoid nests are a characteristic feature in pancreatoblastoma, while they are absent in ACC.[11] Immunohistochemical features may prove vital to confirm the diagnosis. Further differential diagnosis from a pancreatic neuroendocrine tumor is also assisted by immunohistochemistry.[7] However, confirming the diagnosis of an ACC is challenging even in the most experienced centers, mainly due to the rarity of cases and its resemblance to the much most common pancreatoblastoma.

There is no consensus about the optimum treatment from pediatric ACC. Surgery is considered the main treatment. This is largely depicted in the difference in outcomes between those with complete resection (R0) and those without it.[4,12] The most common surgical procedure was Whipple's duodenopancreatectomy in all the above series.

Chemotherapy has an unclear role, but it is generally administered in all cases. The regimens vary from pediatric protocols to adult protocols. Common drugs of choice are gemcitabine and 5-fluorouracil. In our case, a variety of chemotherapy regimens were used, but only PLADO offered our patient a transient partial remission. Furthermore, the role of radiotherapy is also unclear. In our case though, it does not seem to have been proven beneficial for our patient.

The prognosis of patients with ACC is generally ominous. Mortality varies from 27.5%[7] up to 50%[2] in the literature. In USA, the 5-year overall survival rate was 64.8%. However, this rate drops in the presence of distant metastases. Median overall survival for patients with metastatic exocrine carcinomas was 7 months. [4] This prognosis was confirmed in our patient, who survived only 9 months after diagnosis.

Given the rare occurrence of new cases, the design of prospective studies is nearly impossible. The development of mutual database and mutual protocols in continental – or even global – level may be the solution to this problem. In our case, the assistance and experienced guidance of EXPeRT group provided us with the necessary information and access in order to offer our patient the best possible care.

5. Conclusion

Acinar cell carcinoma of the pancreas is a rare type of pediatric cancer. The diagnosis and treatment of ACC can be very challenging. The published literature is limited due to the rarity of this entity. The established network between centers and health providers is essential in managing such rare and complex cases. Surgery is considered the treatment modality of choice as depicted by the difference in outcome between those who underwent complete resection (R0) and those who did not. The unclear role of chemotherapy and radiotherapy, as well as the lack of a "gold standard" regimen, highlights the necessity of multicentral and multidisciplinary teams in order to obtain as much experience as possible in managing with this extremely rare tumor. We consider the cooperation at European – even global – level and multicentral management of those rare cases vital for the optimum outcome of those patients.

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