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RESEARCH

Adult Pancreatic Neuroblastoma, an Unusual Site and Fatal Outcome

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Abstract In this report, we describe a classic case of stroma rich neuroblastoma, nodular type in a 22 year old female presented with a pancreatic mass. This rare and unusual presentation elicits several differential diagnostic categories including solid pseudopapillary tumor, pancreatic endocrine tumor, pancreatoblastoma and PNET. In this report, we tried to differentiate between them depending on the histopathological features and using panel of epithelial and neuroendocrine markers. Although of the rarity of pancreatic neuroblastoma as a primary site of origin, however it should be considered in the differential diagnosis of pancreatic masses in children and young adult. Neuropil and ganglionic differentiation are helpful features to recognize neuroblastoma and differentiate them from other small blue cell tumors. The fatal outcome of adult neuroblastoma confirming the independence of age as a prognostic factor in this neoplasm regardless of stage and histology.

Keywords Neuroblastoma · Pancreas · Fatal outcome

Introduction

Neuroblastoma is a malignant tumor arising from neural crests and is related mainly to sympathetic chain ganglia with affection of adrenal gland in 35% of cases and similar percentage for paraspinal ganglia. In all of these cases, the presentation is mainly with abdominal or retroperitoneal masses. However affection of other sites like pelvis, mediastinum and neck was also reported [1]. Neuroblastoma with an unknown primary was reported in 10% of cases [2]

Neuroblastoma is the main round blue cell tumor affecting infants and young children [3]. In the current study we present a case of neuroblastoma affecting female 22 years and presented as a mass in pancreatic head that is not preoperatively diagnosed. The patient underwent Whipple operation and then received four cycles of chemotherapy but unfortunately she died after 4 months of her diagnosis.

In this report, we discussed the different diagnostic challenges and reviewed the different studies considering neuroblastoma in pancreas.

Case Report

In this report, we describe a case of a 22 year old female complaining of recurrent upper abdominal pain. Ultrasound and CT revealed large pancreatic mass involving the head. The patient underwent Whipple pancreatectomy which is formed of distal gastrectomy, duodenectomy, cholecystectomy and partial pancreatectomy. Gross examination revealed nearly total replacement of pancreas by large mass measuring 7×7×6 cm (Fig. 1). The cut section revealed lobulated appearance with areas of haemorrhage and necrosis (Fig. 1). 15 lymph nodes were dissected including paracystic lymph nodes and all showed reactive changes. Microscopic examination of pancreatic mass revealed an invasive tumor formed of lobules separated by fibrous septa (Fig. 2). The lobule is formed of sheets of small round blue

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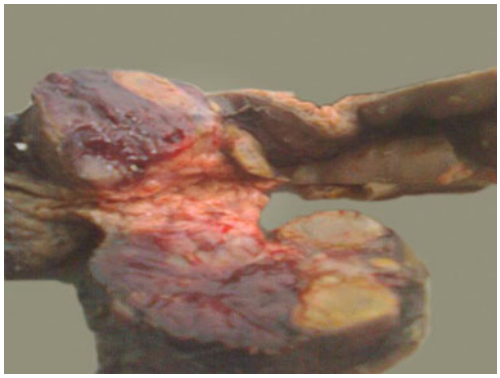

Fig. 1 Gross image of pancreatic mass revealed lobulated large mass with areas of haemorrhage and necrosis

cells entangled in neurofibrillary background (Fig. 2) admixed with areas of necrosis, calcification and cholesterol deposits (Fig. 3). One nodule showed ganglioneuroma separated abruptly from the previously described growth (Fig. 3). The neoplasm was confined to pancreas, not invading any adjacent structures. The neoplastic cells were strongly positive for chromogranin (Fig. 4) while S100 immunostaining stained the neuromatous areas and the supporting cells surrounding the nests of small blue cells (Fig. 4). The tumor cells are completely negative for CK19, CK7, pan CK and CD99 (Fig. 4) while it showed N-myc amplification. The tumor was graded according to Shimada system into neuroblastoma stroma rich, nodular type and into ganglioneuroblastoma, nodular type according to INPC. According to international neuroblastoma staging system, the case was staged as stage I because the tumor was confined to pancreas with negative lymph nodes. There was no previous or family history of similar condition. The patient died after receiving four cycles of chemotherapy which consisted of cyclophosphamide (150 mg/m^2) taken in days 1–7 and doxorubicin (35 mg/m^2) taken in days 8. This regimen was repeated every 3 weeks.

Discussion

In this case, we present an example of an adult neuroblastoma, that unusually affects people beyond age of children, but it is reported in several studies and even in older age than that seen in ours (22 years) such as that reported in Tsujip's et al. study [4] where their patient was 52 years.

Pancreas is a very rare site of neuroblastoma which is commonly arising in the abdomen either in adrenal or extra-adrenal sites, however to our knowledge only three studies reported pancreas as one of primary sites of neuroblastoma. According to **Vouriot** et al., 1985 [5] and Hoeffel et al., 1991 [6], their patients were children presented with masses affecting the tail of pancreas. While according to Kumar et al., 2010 [7], their patient was a fetus 36 week age of gestation who was born by caesarian section and underwent distal

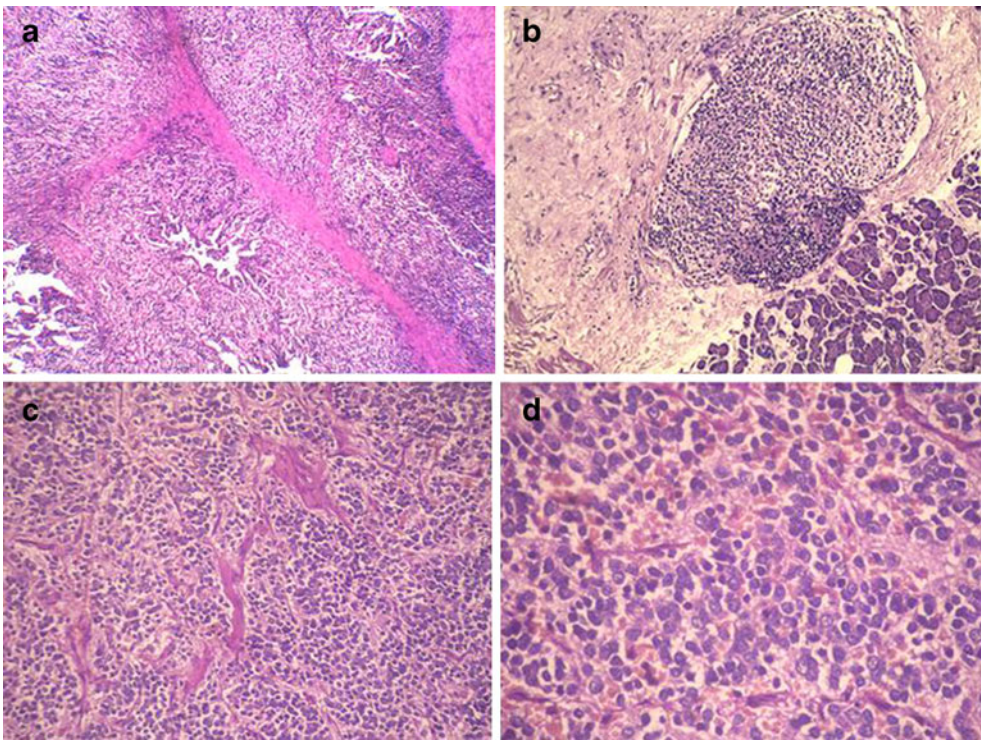

Fig. 2 The neoplasm is arranged in nodules separated by fibrovascular septa (**a**). One of the neoplastic nodule invading the adjacent pancreatic tissue (**b**). The tumor cells are small blue cells slightly arranged in nests entangled in neurofibrillary background with increased vascularity (**c** & **d**) (Haematoxylin and eosin staining)

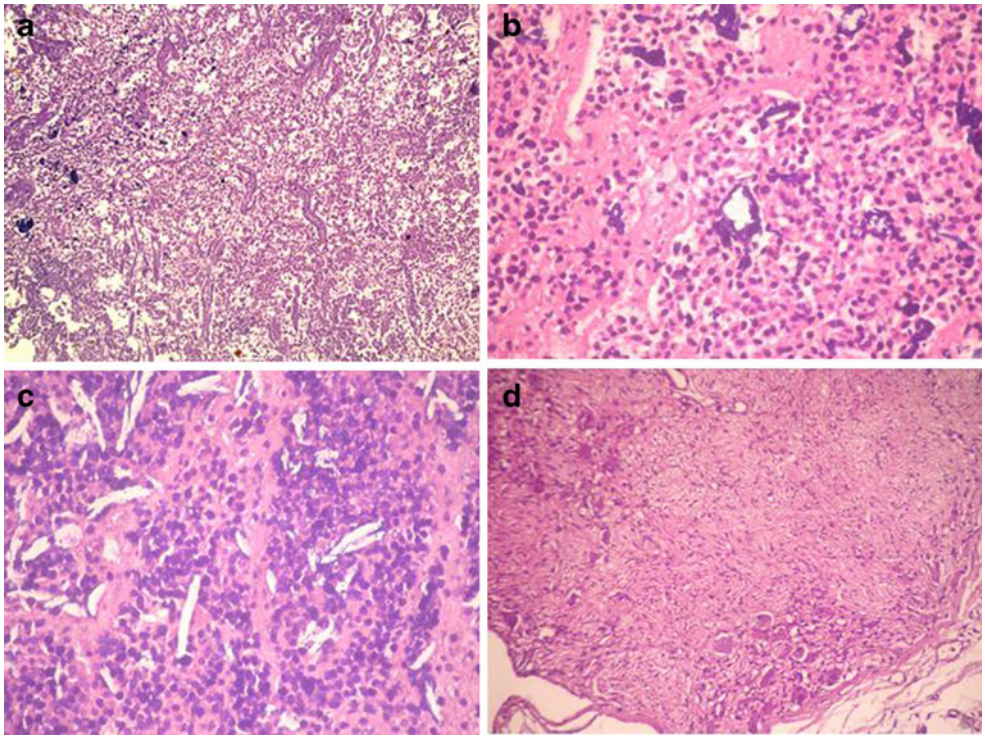

Fig. 3 Another areas of the tumor showing extensive necrosis (**a**), calcification (**b**), cholesterol crystal deposits (**c**) and nodule showing ganglioneuroma characterized by neuromatous stroma and collection of mature ganglion cells (**d**) (Haematoxylin and eosin staining)

pancreatectomy for a mass proved to be neuroblastoma. In the studied cases by **Vouriot** et al. and Hoeffel et al., including our case, neuroblastoma would not be diagnosed or suspected preoperatively.

In our case, the main differential diagnostic categories were solid pseudopapillary tumor, pancreatic endocrine tumor, pancreatoblastoma and PNET (Table 1). Solid pseudopapillary tumor was suspected because of young

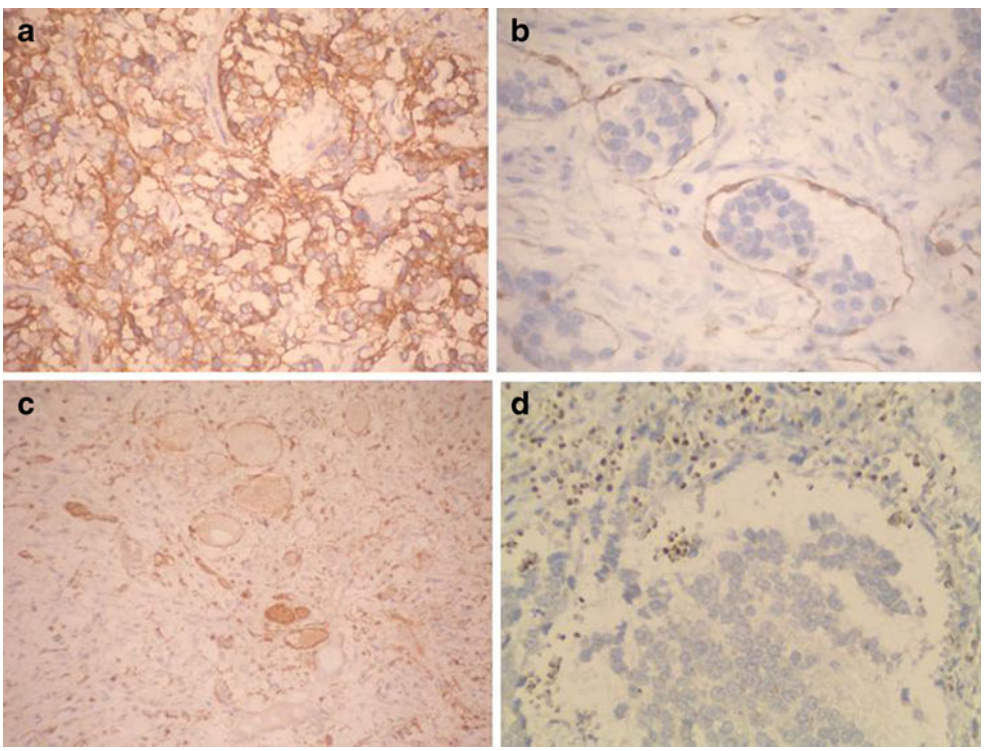

Fig. 4 Diffuse and strong positivity for chromogranin (**a**), S100 immunoreactivity in the stroma surrounding the tumor nests in neuroblastic areas with diffuse positivity in ganglioneuromatous areas (**b** & **c**). The neoplastic cells did not express CD99 (**d**) (Immunohistochemical staining)

Table 1 The differentiation between the main five categories considered in the reported case as regards clinical, gross, microscopic and immunohistochemical data

	Solid pseudopapillary	Endocrine tumor	Pancreatoblastoma	PNET	Neuroblastoma
Age	Young	Any age	Children and may affect second decade	Young	Children but can occur in adult
Sex	Female	Male > female	M:F ratio of 1.3:1	Male > female	Both sexes equally
Site	Any part of pancreas	Mainly tail of pancreas	50% head and 50% for both body and tail of pancreas	Any part of pancreas	Pancreas is a rare site, but tail is the main reported site
Nodularity or lobulation	Present	Absent	Present	Present	Present
Size	Large	Small size not exceeding 5 cm	Large	large	large
Necrosis and haemorrhage	Present	Absent	Present	Present	Present
Calcification	Present	Absent	Absent	Very rare	Present
Microscopic	Solid, cyst, pseudopapillary	Solid, trabeculae, glandular, gyriform, pseudorosette, nests	Epithelial elements arranged in ducts and acini with squamoid corpuscle	Small blue cells not associated with neuropil and ganglionic differentiation is very rare	Small blue cells entangled in neuropil and could be associated with ganglionic differentiation
Epithelial markers	Positive for acinar markers. Ck is positive in 30–70% with keratin profile of ductal cells (CK 7, 8, 18 and 19)	Positive	Positive for acinar and ductal markers	20% express low molecular weight CK	Negative
Neuroendocrine markers	+ve for NSE but not chromogranin	Positive	Positive	Positive	Positive
CD 99	Negative	Negative	Negative	Positive	Negative

age, female gender, large lobulating necrotic and haemorrhagic mass, small to medium-sized neoplastic cells, the presence of cholesterol deposits and calcification. However, it is excluded by absence of pseudopapillary areas and diffuse positivity for chromogranin, as solid pseudopapillary tumor may show positivity for neuroendocrine markers mainly NSE but not chromogranin [8] (Table 1).

As regards pancreatic endocrine tumor, it is included in the differential diagnosis because it affects any age including children and adult, diffuse positivity for chromogranin and microscopic picture that show nesting pattern and increased vascularity. But the large size of the tumor and the negativity for epithelial markers exclude this diagnosis [9] (Table 1).

Although pancreatoblastoma may be considered because of age and similarity to gross picture as regards lobulation, necrosis and hemorrhage. However, it is rapidly excluded because of dissimilarity on microscopic evaluation. As it usually showed epithelial nature of cells arranged in acini or ducts recapitulating normal pancreatic tissue, beside the presence of the characteristic squamoid corpuscle and not small blue cell tumor [10] (Table 1).

Considering PNET and neuroblastoma, they are close entities and can affect the pancreas with a slight more cases reported for PNET [11–15]. However, the presence of neuropil and calcification are against PNET, in addition ganglionic differentiation is very rare in PNET and of course the negativity for CD99 excludes any more possibilities for PNET[15] (Table 1).

Pancreas is more commonly to be a metastatic site for neuroblastoms especially for cases arising in the left adrenal gland and different studies reported neuroblastoma metastasizing to pancreas [16, 17]. According to Fishman et al., 2007 [18], the initial manifestation of stage IV neuroblastoma could be pancreatitis which is explained by invasion of pancreatic parenchyma with tumor cells obstructing pancreatic duct resulting in pancreatitis. In our case, we have no evidences of primary tumor any where suggested by investigations, intraoperative data and lack of previous history of neuroblastoma or ganglioneuroblastoma, so, we considered the case of primary pancreatic origin. In some cases, the primary origin of neuroblastoma is unknown [2]. Some investigators demonstrated the presence of neural crest cells in pancreatic tissue as a source of neuroblastoma [19] and others determined the time of their arrival to the developed pancreas at 26–27 somite stage [20]. Neural crest cells were reported to colonize dorsal pancreas prior to

ventral pancreas and they are the sole source of pancreatic neurons and glia [20]. Long time ago, some authors believed that pancreatic islets cells were of neural crest origin [21] but currently it is proved to be of endodermal origin [22] and neural crest cells are required for beta cell maturation [20]. According to Kumar et al., pancreas may carry a supportive environment for neural crest derived neuroblasts and provide the developmental factors required for neuroblastoma progression [7].

Although the course of adult neuroblastoma may be longer compared to pediatric age group, however, the outcome is poor and this is reported previously [4, 23]. Although our case was presented in early stage but she died after about 4 months of operation and receiving four cycles of chemotherapy, which again confirmed the independence of age as a highly prognostic factor in neuroblastoma. The unfavorable histology of the nodular type of stroma rich neuroblastoma may share in the fatal outcome of our case and other similar cases [24]. In addition, N-myc amplification was one of the molecular events associated with dismal prognosis [25] and unfortunately our patient experienced this amplification.

In Conclusion

Although of the rarity of pancreatic neuroblastoma as a primary site of origin, however it should be considered in the differential diagnosis of pancreatic masses in children and young adult. Neuropil and ganglionic differentiation are helpful features to recognize neuroblastoma and differentiate them from other small blue cell tumors. The fatal outcome of adult neuroblastoma confirming the independence of age as a prognostic factor in this neoplasm regardless of stage and histology.

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