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Rare Pancreatic Tumour in a 16-Year-Old Girl: a Case Report

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A 16-year-old girl was admitted to a hospital after having noticed clearly palpable abdominal mass, without accompanying symptoms. At surgery a tumour superficially attached to the pancreatic tail, well-encapsulated, measuring approx. 8x5x3 cm, had been found and resected. Histological examination using routine hematoxylin and eosin staining, additional histochemical and immunohistochemical techniques revealed low-grade tumour with mixed appearances of PSEN and pancreatoblastoma; both of these tumours originate from pancreatic primordia.

Introduction

Neoplasms of exocrine pancreas in childhood and early adolescent period are quite rare and often difficult to diagnose because of their uncommon histological appearance. We present here one of such cases.

A Case Description

A female patient age 16, petite, presented to a hospital after having noticed a strange, painless mass in her abdomen. This mass was not accompanied by any symptoms due to compression of viscera and vessels or to improper or excessive hormonal activity. At surgery a tumour located superficially close to pancreatic tail had been found and resected; a major portion of the tumour was placed in the large omentum. The tumour measured 8x5x3 cm (approx. 3x2x1 in) and weighted 140 g (approx. 5 oz). The tumour was encapsulated, removed as a whole, without stalk; soft, brownish-red, velvety, with neither signs of degenerative changes nor areas of hemorrhage; close to the capsule areas of solid but soft, whitish tissue about 1 cm (approx. 3/8 in) thick, had been found. In postoperative course increased levels of amylase in tumour bed lavage were found, showing its connection with pancreatic tissue. No enlargement of regional lymph nodes or other signs of tumour spreading were noticed.

At microscopical examination papillary structures built of quite uniform, high (cylindrical) cells with high-placed nuclei predominated; there were myxoid changes in stroma clearly demonstrated in PAS staining. The tissue was more solid at the capsule, nevertheless still with the presence of pseudopapillary and trabecular structures. In those areas foci of oval to round cells with abundant, pale cytoplasm were present; these cells did not show reactivity with anti-CD68 antibody and were probably degenerating tumour cells. There was marked mitotic activity (up to 8 mitoses per 10 HPF), with no atypical mitoses present. Between the papillae there were dispersed groups of round to oval, hyaline bodies, being stained uniformly with eosin and showing positive reactions in PAS and PAS-D methods and with anti-α-1-antitrypsin antibody.

In some instances the tumour seemed to invade capsule and large omentum, with no evidence of embolisation of capsular vessels. In the tumour vicinity a focus of ectopic spleen tissue and one reactive lymph node were found.

Results of additional immunohistochemical and histochemical staining are shown in Tables.

Discussion

Primary tumours of exocrine pancreas are extremely rare in young people. Benign tumours of acinar tissue (*cystadenoma*, *adenoma acinare*) are rare in adults and seem not to be observed in children. Warthin [12] in 1952 described embryonal carcinoma in a 15-month-old boy and cited eight cases of carcinomas and two pancreatic lymphosarcomas diagnosed previously in children. Frable et al. [2] described specific type of pancreatic carcinoma in an infant as "papillary carcinoma of infant pancreas". Microscopically two patterns are seen: sheets of small hyperchromatic

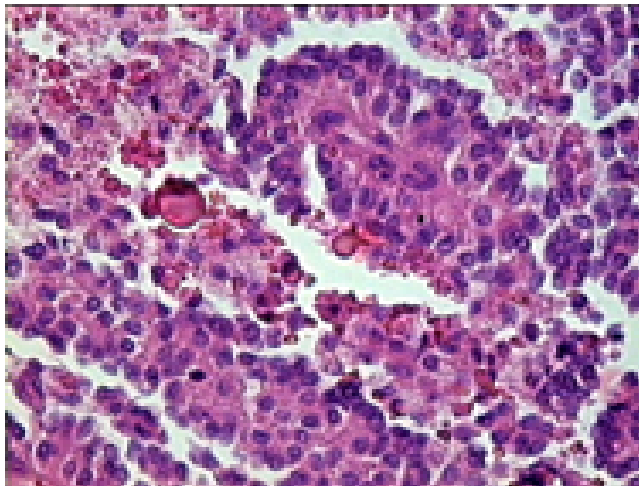

Fig. 1. Hyaline globules in papillary component of the tumour. HE. Magn. 200×.

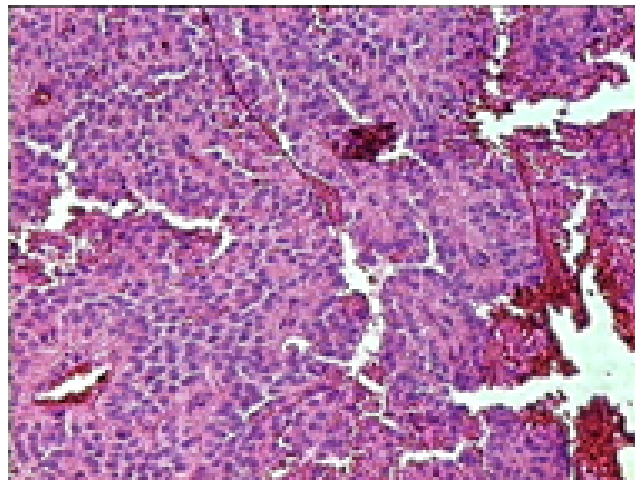

Fig. 2. Solid and trabecular component of the tumour. HE. Magn.100×.

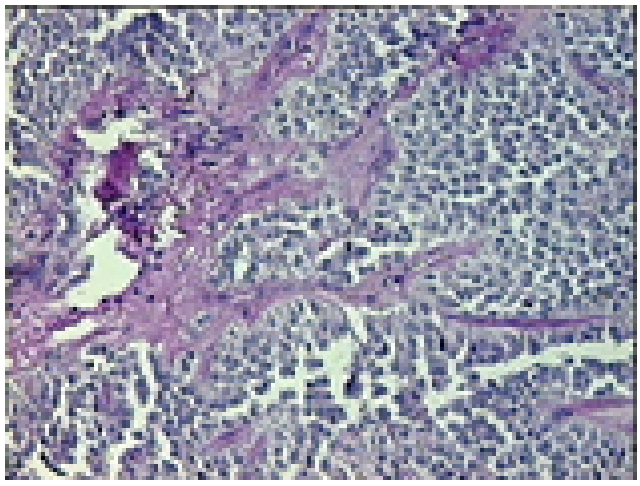

Fig. 3. Myxoid changes in papillary stroma. PAS. Magn. 100×.

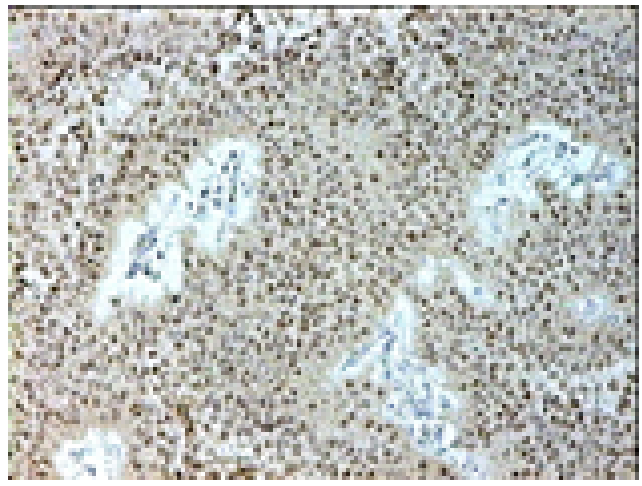

Fig. 4. Progesterone receptor in tumour cells. Magn. 100×.

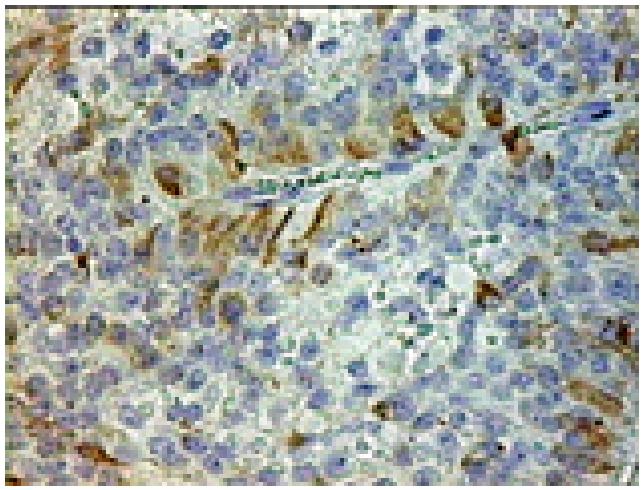

Fig. 5. Cytokeratins (pancytokeratin) expression in papillary portion of the tumour. Reactivity seen in certain cells only. Magn. 200×.

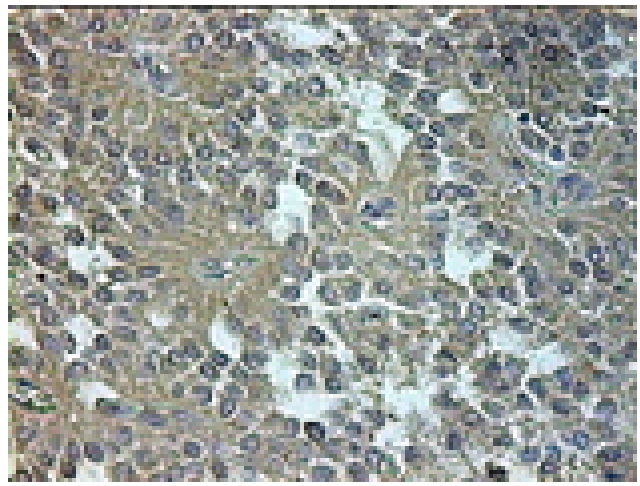

Fig. 6. α-fetoprotein expression in papillary portion of the tumour. Magn. 200×.

cells and areas in which cells are arranged in acinar pattern. In electron microscopy no excretory granules were demonstrated [5]. From today's point of view those observations have mostly historical importance; nevertheless they point to a similarity of pancreatic tumours in childhood and difficulties in their differential diagnosis.

Table 1
Immunohistochemistry of given tumour compared to ICT* [3]

Antibody	% ICT cases	No. of cases	Range	Analyzed case
CALBINDIN28	100	2	N/A	not applied
CD117	100	1	N/A	not applied
CD56	100	1	N/A	not applied
DPC4_SMAD4	100	1	N/A	not applied
MMP-2	100	21	N/A	not applied
MMP-9	100	21	N/A	not applied
TIMP-1	100	21	N/A	not applied
TIMP-2	100	21	N/A	not applied
NSE	99	134	97–100	diffuse +
SYNNAPTOPHYS	99	58	95–100	++
KERATIN-LMW	88	8	65–100	–
CHROMOGRANA	76	66	66–87	diffuse +
KERATIN-PAN	67	12	40–94	focal +
GLUCAGON	61	28	43–79	not applied
CD68	60	5	18–100	–
INSULIN	58	28	39–76	not applied
NFP	53	21	32–74	not applied
CA 15-3	50	6	10–91	not applied
CD99	40	20	19–62	–
HPP	40	28	22–58	not applied
SEROTONIN	37	11	8–65	not applied
HCG-ALPHA	33	205	26–39	not applied
CDX-2	29	14	5–53	not applied
VIMENTIN	24	13	1–46	+++
CK 20	13	8	0–36	not applied
GASTRIN	4	28	0–11	not applied
VIP	4	28	0–11	not applied
CA 19-9	0	6	N/A	not applied
CALRETININ	0	2	N/A	not applied
CD5	0	8	N/A	not applied
GFAP	0	1	N/A	not applied
GGT	0	1	N/A	not applied
HBME-1	0	6	N/A	not applied
HEPPAR-1	0	10	N/A	not applied
MELAN-A103	0	4	N/A	not applied
MESOTHELIN	0	11	N/A	not applied
MITF	0	4	N/A	not applied
RCC MA	0	4	N/A	not applied
TTF	0	15	N/A	not applied

*ICT = Islet Cell Tumour

Table 2
Other stains made

Progesterone receptors	++
CD 34	–
AFP	focal +
CEA	–
IGF	–
PAS-D	see text
Ag impregnation	–
EMA	–
A-1-AT*	+++

*α–1-antitrypsin

Papillary and solid epithelial neoplasm (PSEN) is sometimes described as "solid and pseudopapillary tumour", "papillary and cystic tumour", "solid-cystic-papillary epithelial neoplasm" etc., depending on proportions of its components; recently it has been termed Gruber-Frantz tumour [11]. It is most often found in young women (less frequently in girls, mature women and in men), when palpable abdominal mass is the main symptom. Some of these tumours are found after trauma causing bleeding from damaged tumour tissue; some of them cause symptoms like abdominal pain or discomfort. Grossly such tumours are often large and can show foci of hemorrhage and necrosis on cross sections. Degenerative and hemorrhagic changes are usually caused by poorly developed stroma with tumour supplying vessels. Most of these neoplasms are well encapsulated at least at some portions of the tumour surface, but in some instances borders are typical for a solid infiltrating tumour. Rarely, such tumour was found in structures adjacent to the pancreas, but separated from it anatomically.

Microscopically these are tumours rich in cells and have some similarity to islet cell tumour (ICT); their most characteristic feature is a presence of pseudopapillary structures covered by some layers of epithelial cells with pale to eosinophilic cytoplasm, lacking of glycogen and mucin. PAS-positive spherical intracytoplasmic inclusions are often present. In some cases clustering of foam macrophages and foreing body-type giant cells close to lipoid crystals is observed. The nuclei are oval and corrugated, some of them can be enlarged or irregular, nucleoli are small and unconspicious, mitoses usually infrequent. Hyaline globules can be also present. Coarse fibrotic and vacuolated stroma often shows marked myxoid changes, which is of diagnostic importance. In electron microscopy signs of acinar, ductal and sometimes endocrine differentiation can be seen; immunohistochemical methods show presence of keratin, desmoplakin, pancreatic enzymes and vimentin; moreover, focal expression of NSE and α-1-antitrypsin can sometimes be demonstrated. In some papers also expression of pancreatic hormones was shown [6], which proves that PSEN is derived from pancreatic primordium with predomination of exocrine differentiation but with ability of bidirectional differentiation. Progestagen receptors were found immunohistochemically and by adsorption on dextran-covered activated coal [8, 13], which suggests (together with more frequent development in young women) hormonal dependence of the tumour [9, 11].

Pancreatoblastoma is the term used for a group of quite pleomorphic tumours, described as encapsulated masses capable to spread from pancreatic tissue. It is most common neoplasm of the pancreas in children, more often observed in boys than girls, sporadically arising in adults, often confused with PSEN. It is usually encapsulated with mean diameter of 10 cm (approx. 4 in). The course is indolent but malignant [4]. Cut surface is yellow, white, gray or brown; firm, sometimes lobulated; cystic, hemorrhagic and necrotic changes are often noted. This is a cellular tumour, composed of small to medium-sized cells, elongated or polygonal with oval nuclei, forming solid sheets, masses and trabeculae, sometimes also small glands or ducts. Ultrastructurally presence of zymogen (ca 400 nm) or much smaller (ca 100 nm) neuroendocrine granulations was demostrated [10]. There are signs of lobular, endocrine and canalicular differentiation, with expression of pancreatic enzymes (incl. α-1-antitrypsin [10]), endocrine markers (incl. NSE) and CEA. Moreover, presence of AFP in tumour tissue as well as in the blood was demonstrated. The presence of nodules composed of squamous epithelium is likely to be very characteristic [4]; in some papers cytokeratin expression was also shown [10]. Stroma can be abundant, sometimes cellular. Local recurrences and metastases, especially to the liver, are also possible [9, 11]. Diversity of differentiation reflects developmental abilities of pancreatic primordium at stage earlier than 14th week of gestation [4], confirming origin from blastemal cells with bidirectional differentiation abilities [10].

Islet cell tumour (ICT) is sporadic, mostly microscopic finding in about 1% of routine autopsies; most of such tumours arise in adults, nevertheless they can be also found in children and even infants. Histological signs of secretory abilities are unknown. Because of unpredictable biological behaviour of these tumours and histological pattern similar to intestinal carcinoids many terms are in use (a term "endocrine pancreatic tumour" is being proposed as the less confusing). They can manifest as palpable abdominal mass, can also cause pain or jaundice or other symptoms correlated with hormones secreted; it is to be mentioned that se-

cretion of hormones does not correspond to tumour size; ICT without hormonal activity seldom causes any clinical symptoms, thus, tumours of clinical significance have diameter from ca 1 cm (approx. 1/2 in) up to ca 15 cm (approx. 6 in) or more [11]. Forshall described an apparently "silent" ICT weighting over 1 kg (approx. 2 lb) removed from the pancreas of a 9.5-year-old girl [1]. Most of these lesions are single, but presence of two or more tumours suggests possibility of multiple endocrine neoplasia (MEN) syndrome, usually of type 1 [11].

Grossly these are usually masses encapsulated partially or in total, stained depending on quantity of the stroma, vascularization, cellularity and lipid accumulation, thus from grayish-beige to pinkish and red to yellow. Macroscopic appearance can mimic spleen tissue or intra-pancreatic lymph node. Fibrosis is sometimes marked. Rarely, cystic degeneration and sometimes haemorrhage are seen [9, 11]. Larger tumours, of apparently longer development period, consist of larger amounts of fibrous tissue and can even contain calcifications and bone tissue [9].

Microscopically three main patterns are observed, in combinations or alone: a) trabecular/labirynth, b) lobular/ductular, c) solid/diffuse/medullary. Other patterns were also described [7]. Cells are usually round or cuboid to polygonal, with centrally placed nuclei, have eosinophilic or amphophilic cytoplasm, finely granular, and are quite uniform; sometimes are elongated, especially in trabecular patterns, with long axis of the cell perpendicular to the axis of the trabecula. Nuclei are rather round in round cells and elongated in high ones. Cells are usually small- to medium-size, rarely large [9, 11]. Often argyrophilic granules can be demonstrated. Tumours are sometimes rich in neutral fats and thus their cytoplasm can have foam appearance. In some cases PAS-positive granules located intra- or extracellularly, composed probably of α-1-antitrypsin, can be also demonstrated. Amyloid deposits are also possible, though they are most common in insulin-secreting tumours [11]. There is often expression of α- or β-hCG [9].

In our case a papillary histological pattern with papillae covered with single-layered cylindrical cells predominates all over the tumour; mitoses were frequent, no polygonal cells were present; there were also areas of clear cells of uncertain origin and areas of trabecular cells arrangement. The tumour was well-encapsulated and seemed not to be connected with pancreas. No hemorrhage, necrosis or cystic changes were found, there were only myxoid changes in the stroma. Cytokeratins were present only focally. Tumour cells expressed α-1-antitrypsin, vimentin and progesterone receptor; there were also signs of neuroepithelial differentiation, but they were unspecific. Expression of CEA was absent and AFP was shown only focally (without elevated serum AFP levels).

All these features together with clinical data (sex, age, symptoms) suggest that in differential diagnosis papillary and solid PSEN variety with some signs of neuroendocrine differentiation and increased mitotic activity are to be taken into account; observed features can be also found in pancreatoblastoma.

Histological pattern (papillae with well vascularized stroma), as seen in our case, can suggest neuroendocrine-derived lesion, but the main cell type is high (cylindrical) cell of glandular epithelium. Biochemical signs of neuroendocrine differentiation can be found also in PSEN.

Conclusion

In the tumour described above mainly elements of structure typical of PSEN and pancreatoblastoma were found; these are: good tumour demarcation, rich vasculature, prominent expression of progesterone receptor, with barely marked recessive changes. There was also lack of full spectrum of neuroendocrine activity of the tumour. Increased mitotic activity and some signs of penetrating of tumour capsule, though observed in PSEN as well as in pancreatoblastoma, are worrisome.

Both tumours have appearance of a lobular-canalicular neoplasm arising from undifferentiated pancreatic primordia [4].

Some of the histological and biochemical signs suggest derivation of the tumour from islet cells. Panel of immunohistochemistry usable in ICT cases is shown in Table 1, comparing it to reactions applied in our case [3]. Tumour location together with its definitely papillary pattern and cytological characteristics rule out the diagnosis of ICT. Moreover, there was strong expression of progesterone receptor (see Table 2), which is uncommon in neuroendocrine tumours and characteristic for PSEN, found also in pancreatoblastoma.

The presence of mixed histological features of pancreatoblastoma and PSEN with similarity of clinical signs and course suggest that they constitute some *continuum* and are to be regarded as subsequent phases of differentiation of the lesion or tumours at different stages of differentiation but originating from the same embryonal cells. To confirm or exclude such suspicion more studies, perhaps extensive retrospective surveys, are needed.

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