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Ovarian-like stroma in an invasive mucinous cystadenocarcinoma of the pancreas positive for inhibin. A hint concerning its possible histogenesis

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Abstract A female patient with a mucinous cystadenocarcinoma originating from a mucinous cystadenoma of the pancreas is presented. The cystic tumour was diagnosed 3 years before and was treated with interventional external and internal surgical drainage before radical resection was accomplished by left hemipancreatectomy. Histology showed simultaneous occurrence of mildly dysplastic and invasive malignant epithelium. Immunohistology revealed inhibin-positive cells in the ovarian-like stroma of the tumour. The demonstration of ovarian-like stroma positive for inhibin suggests that this could be a hamartoma with dispersed sex-cord stroma, which would explain the predominance of the female gender in mucinous cystic tumours of the pancreas.

Key words Pancreatic cystadenocarcinoma · Inhibin · Ovarian-like stroma

Introduction

Mucinous cystic tumours are uncommon pancreatic neoplasms [5, 16, 17, 21, 24]. The peak incidence of these tumours is between the fourth and seventh decades, with a marked predominance of the female sex [6, 19, 22, 23]. We describe the case of a female patient in whom a mucinous cystadenocarcinoma originated from a mucinous cystadenoma. Immunohistology showed ovarian-like stroma positive for inhibin. Inhibin, a heterodimeric peptide hormone normally produced by ovarian granulosa cells to modulate folliculogenesis, has proven to be a sensitive marker of primary and recurrent adult granulosa cell tumours of the ovary and can be demonstrated immunohistologically with monoclonal antibodies after fixation and wax embedding [2, 14]. Inhibin has been discussed as a tumour marker for ovarian carcinomas [3] and has not previously been demonstrated in cystic neoplasms of the pancreas.

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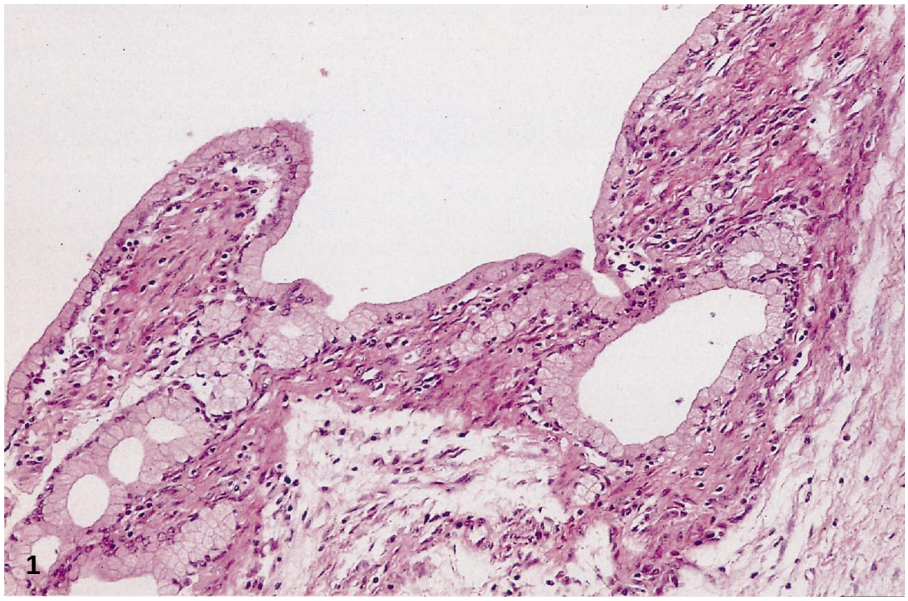
Case report

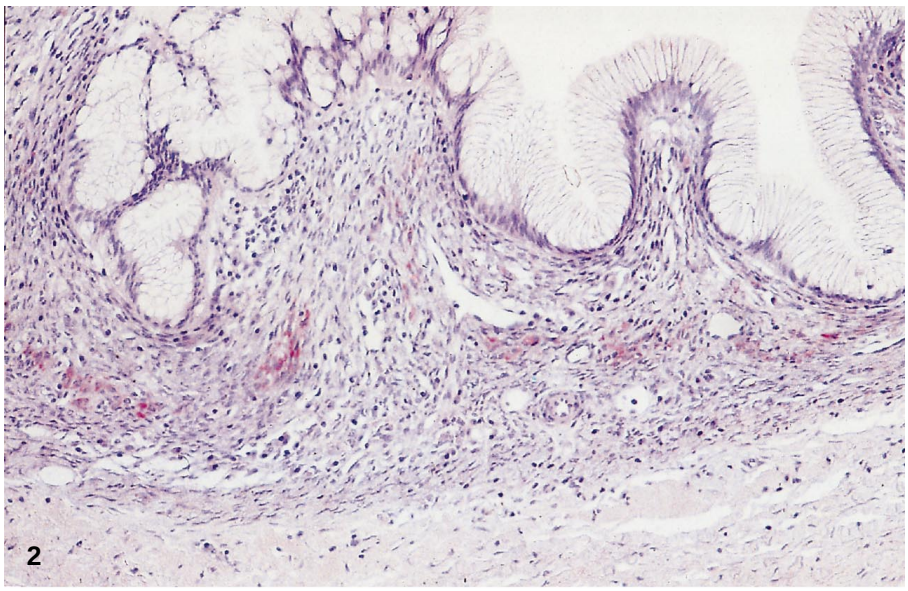
A 48-year-old female patient with no previous medical history experienced two episodes of acute pancreatitis of unknown origin within a period of 4 months. Alcohol consumption and bile stones were ruled out as causes of the acute pancreatitis. The first episode resolved spontaneously. As a sequel to the second episode of pancreatitis a pseudocyst developed in the region of the pancreatic body and tail. Over the next 2 years the size of the cyst gradually increased though the patient was asymptomatic. It measured 10 cm in diameter and displaced the stomach, the duodenum and the pancreatic duct system, as demonstrated by ultrasonography, gastroscopy, and endoscopic retrograde cholangio- and pancreatography. Puncture of the cyst revealed a serous liquid with a lipase concentration of 69,000 U/l and amylase concentration of 2,500 U/l. Transcutaneous ultrasound-guided drainage of the cyst was performed via a pigtail catheter. The patient developed fever and abdominal pain and was transferred for surgery in another hospital with the diagnosis of an infected pancreatic pseudocyst. Subsequent laparotomy revealed a cyst located in the pancreatic tail, which was filled with 700 ml of pus. A marked inflammatory reaction of the pericystic tissue was noted. After marsupialisation the cyst was drained externally via a Foley catheter. The patient's condition rapidly improved, and the drain was left in place for 6 months. Though the patient was free of symptoms, the cyst was nonetheless still present, with a size of 6.4 × 5.5 cm. It contained solid and cystic areas, and the wall was 0.5 cm thick. At that time an internal drainage of the cyst was accomplished in another hospital by means of a latero-lateral Roux-en-Y cystojejunostomy. The cyst was opened at its inferior margin through the mesocolic ligament. Neither the cystic wall nor the contents of the cyst were thought by the surgeon to the neoplastic. No histological or cytological examination was performed. Following surgical drainage

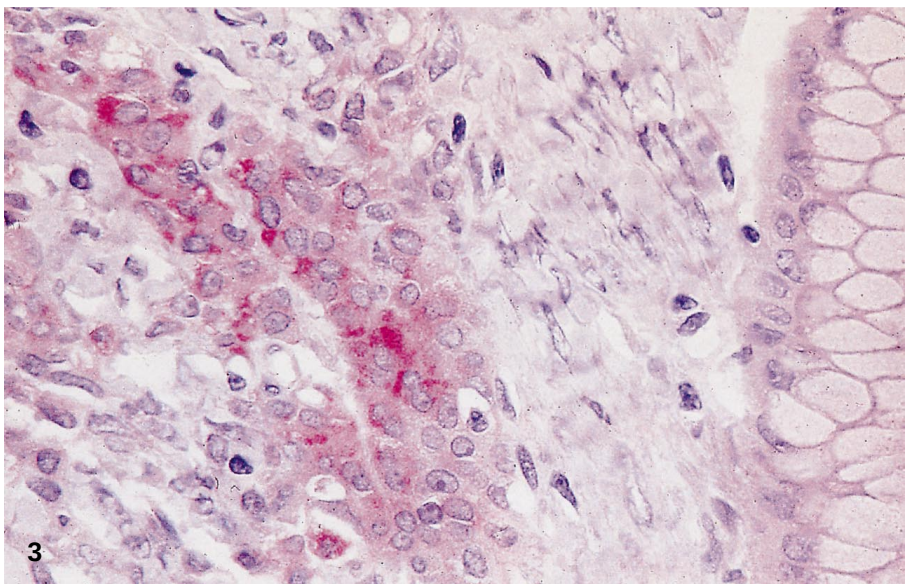
Fig. 1 Mucinous cystadenoma with mildly dysplastic columnar mucinous epithelium with infoldings. H&E, original magnification ×40

Fig. 2 Mucinous cystadenoma with a layer of densely pached spindled cells (ovarian-like stroma) focally positive for inhibin. APAP, original magnification ×40

Fig. 3 Mucinous cystadenoma with inhibin positive specific stroma (ovarian-like). APAP, original magnification ×160







the cyst did not resolve but increased further in size over the next 2 years. Though still asymptomatic, the patient was admitted to our hospital. A cystadenocarcinoma was suspected, and surgical removal of the cyst was planned. By this time, the patient was 51 years old.

Laboratory examinations were normal except for tumour markers, which had not been determined previously; the concentration of CA 19-9 was elevated, at 82.6 kU/l, while that of carcinoembryonic antigen was normal. At laparotomy significant pericystic adhesions were found. An en-bloc resection of the cystic tumour was accomplished by means of left pancreatectomy, splenectomy and adrenalectomy. The Roux-en-Y loop was also resected along with the tumour, and a regional lymphadenectomy was performed. There was no evidence of metastatic tumour spread within the abdomen. The postoperative course was uneventful and the patient was discharged on day 16.

The patient is still alive and well 3 years after the resection. Laboratory tests including CEA and CA 19-9 were normal, and ultrasonography and CT revealed absence of local and distant tumour recurrence at the latest follow-up.

Pathological findings

The histopathological examination revealed a highly differentiated mucinous cystadenocarcinoma within a mucinous cystadenoma. Macroscopically, the entire cystic tumour had a diameter of 10 cm and consisted of multiple cysts and solid areas. On histology, in the solid tumour areas a highly differentiated cystadenocarcinoma was found. The malignant tumour was directly invading the cyst wall and the adjacent serosal and muscular layer of the Roux-en-Y loop. The left adrenal gland and the splenic hilus were closely attached to the tumour but not infiltrated. None of 12 resected lymph nodes was involved, and nor was the pancreatic resection margin. The TNM classification according to UICC 1992 [15] is defined as pT2N0M0, UICC stage I, G I, R 0.

The tumour was characterised by a markedly proliferating columnar epithelium (Fig. 1), which at different localisations comprised of normal epithelium, adenoma, carcinoma, or intermediate stages. Areas of cystadenoma showed a densely cellular band of spindle cells with round or elongated nuclei and scarce cytoplasm (ovarian-like stroma; Fig. 2) which was focally positive for inhibin (APAP; Fig. 3). Immunohistochemical staining with the proliferation marker MIB-1 demonstrates areas with high proliferative activity of the epithelium.

Discussion

Most morphological and clinical findings in this case, and also the course of the disease, are in accordance with previous knowledge of this tumour type. In addition to malignant invasive epithelium, the tumor showed areas with apparently benign columnar cells, making an adenoma–carcinoma “sequence” seem likely. Only 1% of exocrine pancreatic malignancies are cystadenocarcinomas [6, 7, 13, 18, 24]. These tumours are of particular interest because they may present early as isolated episodes of acute pancreatitis, and even in advanced stages they can still be cured by pancreatectomy [10]. Long-term survival is achieved in 50–76% of patients who undergo resection of pancreatic cystadenocarcinomas [16, 23–26]. About two-thirds of such tumours are located in the body or tail of the pancreas [7, 20, 23]. The results of curative resection are significantly better than in the case of ductal adenocarcinomas [8, 10]. Even when residual tumour has been left behind at operation, 5-year survival rates of 14% have been reported [23].

The observation regarding the inhibin positivity of stromal cells of the tumour is novel and our most interesting finding. The demonstration of ovarian-like stroma is interesting with regard to a possible histogenesis of the tumour as hamartoma with dispersed sex-cord stroma. Inhibin, a heterodimeric peptide hormone normally produced by ovarian follicle cells, has been shown to be a sensitive marker of primary and recurrent adult granulosa cell tumours of the ovary [11, 12]. To our knowledge, inhibin has not previously been demonstrated in cystic pancreatic neoplasms. In this context it is noteworthy that cystadenocarcinomas develop predominantly but not exclusively in females. It is known that the ovarian-like stroma is present in low-grade areas of female cystadenomas, whereas it is absent in the infiltrating adenocarcinomatous areas and in all cases occurring in males [27]. These findings raise the question as to whether some of these lesions may derive from true ovarian tissue. Cystadenocarcinomas arising in preexisting cystadenomas of the hepatobiliary tract with a mesenchymal (ovarian-like) stroma have recently been reported [1, 9]. They occurred only in women and had a relatively indolent course in most instances. In primary mucinous cystadenocarcinomas of the retroperitoneum heterotopic ovarian tissue was also found in female patients, and the development of these tumours from ovarian-type teratomas was discussed [4].

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