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Pancreatic large mucinous cystoadenoma with invasive ductal carcinoma in pregnancy. Case report

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SUMMARY: **Pancreatic large mucinous cystoadenoma with invasive ductal carcinoma in pregnancy. Case report.**

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Background. *Cystic tumour of the pancreas are infrequent and malignancy of the pancreas during pregnancy is extremely rare. Mucinous cystoadenomas is the most frequent cystic pancreatic neoplasm and it is seen mainly in women suggesting a sex hormone influence. Its presentation during pregnancy is extremely rare and entails difficulties in diagnosis and therapy.*

Case report. *A 28 year old woman was referred to our service for abdominal mass. She had given birth to her second child two weeks previously. Ultrasound and CT scan showed a large cystic lesion, with sepitation and inner solid growth portions, involved mainly the left sovramesocolic space. An ultrasound-guided aspiration of the cystic fluid showed high level of CEA and CA. 19-9. The patient underwent laparotomic body-tail pancreatectomy and splenectomy. The histological examination showed mucinous cystoadenoma with associated invasive ductal carcinoma, with ovarian-like stroma and a well delimited fibrous capsule. Hystochemical study revealed a strong positivity for progesterone receptors.*

Conclusions. *To our knowledge this is the eighth case of mucinous cystoadenoma reported in English literature and the forth with an invasive adenocarcinoma associated. This pathological entity should always be kept in mind in case of patient with an hepigastric mass during or soon after pregnancy. Aggressive approach is mandatory.*

RIASSUNTO: **Voluminoso cistoadenoma pancreatico associato a carcinoma duttale invasivo in gravidanza: descrizione di un caso clinico.**

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Premessa. *I tumori cistici del pancreas sono rare entità eccezionalmente presenti in gravidanza. Il cistoadenoma mucinoso è la più comune di queste neoplasie; la sua maggiore incidenza nel sesso femminile suggerisce un'influenza ormonale per quel che riguarda la sua genesi. La comparsa di questo tipo di neoplasia in gravidanza è una situazione eccezionale che comporta difficoltà sia diagnostiche che terapeutiche.*

Caso clinico. *Descriviamo il caso di una paziente di 28 anni ricoverata presso la nostra unità operativa per una voluminosa massa addominale. La paziente aveva partorito il suo secondogenito due settimane prima del ricovero. Gli esami ecografici e la tomografia computerizzata avevano messo in evidenza una voluminosa lesione cistica, con setti e gettoni solidi di crescita interni, che interessava lo spazio sovramesocolico sinistro. L'esame del liquido endocistico ottenuto mediante aspirazione ecoguidata aveva messo in evidenza elevati valori di CEA e CA. 19-9. La paziente è stata quindi sottoposta ad intervento chirurgico di splenopancreatectomia distale. L'esame istologico ha messo in evidenza la presenza di un cistoadenoma mucinoso con un carcinoma duttale invasivo associato, con una componente stromale similovarica ed una capsula fibrosa ben delimitabile. Lo studio istochimico ha messo in evidenza una forte positività per i recettori progestinici.*

Conclusioni. *Quello da noi riportato è l'ottavo caso di cistoadenoma del pancreas in gravidanza descritto in letteratura ed il quarto caso in cui vi è associata una componente di adenocarcinoma invasivo. Questo quadro clinico-patologico dovrebbe essere sempre preso in considerazione in una paziente con massa epigastrica in corso o subito dopo la gravidanza. In questi casi l'approccio chirurgico è sempre necessario.*

KEY WORDS: Pancreas - Cystic neoplasia - Cyst - Pregnancy.
Pancreas - Neoplasia cistica - Cisti - Gravidanza.

Introduction

Mucinous cystic neoplasms (MCNs) of the pancreas are rare tumors located almost exclusively in the body or the tail of the pancreas. They occurs predominantly in middle-aged women and present two distinct com-

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ponents: an inner mucinous epithelial layer and an outer dense cellular ovarian-like stromal layer. An invasive adenocarcinoma of the ductal type is associated in about one third of the cases (1,2) . Mucinous cystic neoplasm stromal cells have been shown by immunohistochemistry to be positive for estrogen receptors and progesterone receptors, thus suggesting regulation by sex hormones (3).

MCNs associated with pregnancy are extremely rare; only three cases of pancreatic mucinous cystadenoma and four cases of pancreatic mucinous cystadenocarcinoma have been previously reported (4-10). The diagnosis is often difficult since insidious symptoms and bodly changes during pregnancy may mask the true clinical situation.

We report a case of a 28 year old woman, who was referred to our Institution for abdominal mass due to a large cystic tumour of the pancreas that was noticed soon after delivery. We discuss the main features of this rare condition.

Case report

A secondiparous 28 year old woman was referred to our Institution for a voluminous hepigastric mass noticed soon after her delivery. During pregnancy she complained only abdominal discomfort, that was interpreted as due to compression of the uterus. She had been followed in local hospital during pregnancy, but no abdominal mass had been pointed out. Her family and medical history were unremarkable. The blood and serum chemistry were within normal limits, only the CA.19-9 level was 64,4 U/mL (n.v. < 33.0).

Abdominal ultrasound revealed a large cystic mass of the pancreas with corpuscular fluid and solid vegetations. The mass dislocated forward the stomach and laterally the spleen. A CT scan showed a large cystic mass 16 x 12 cm in diameter with septation and contrast-enhanced inner solid growth portions (Fig. 1).

The mass was in contact with the greater curvature of the stomach, and involved mainly the left sovramesocolic space, pushing downward the transverse colon. It also compressed the ventral edge of the abdominal aorta which was dislocated on the right. Celiac trunk and

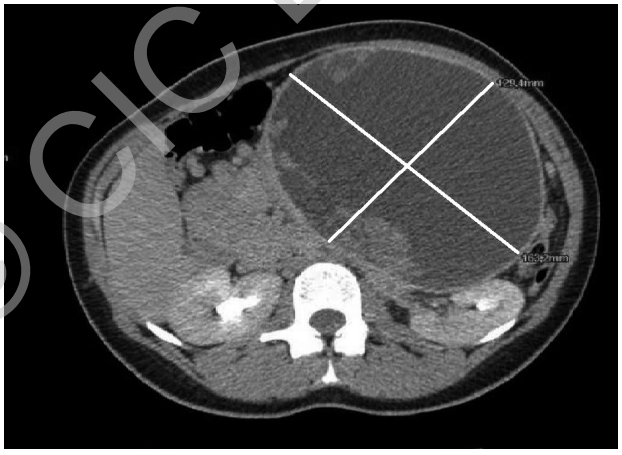

Fig. 1 - CT scan showing a large cystic mass with septation and contrast enhanced in solid growth.

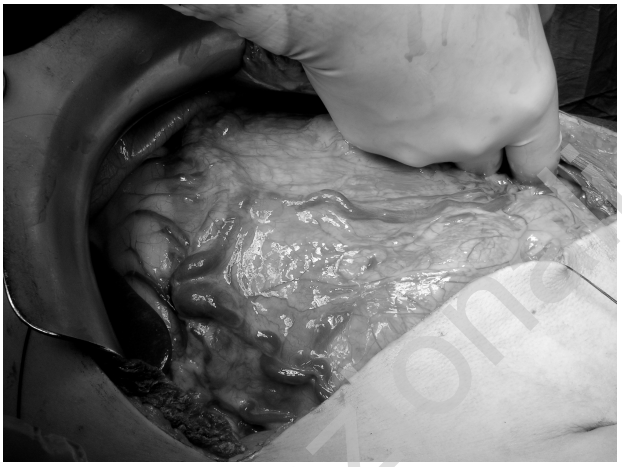

Fig. 2 - Findings of:portal hypertension at laparotomy.

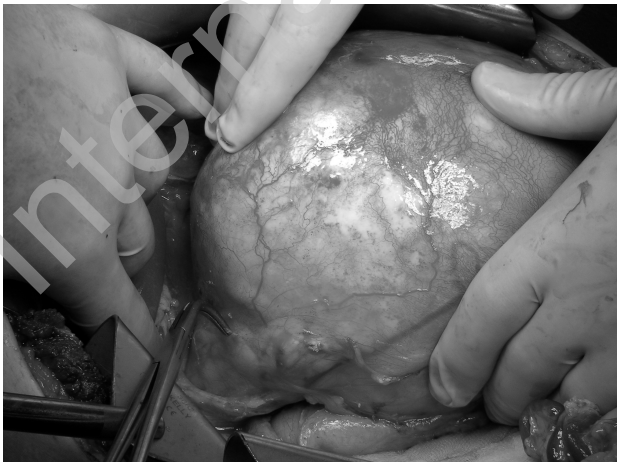

Fig. 3 - Intraoperative finding: a voluminous cystic mass in the tail of the pancreas.

mesenteric superior artery, even though dislocated to the right, took contrast regularly. The mass pushed back the head of the pancreas and the duodenum and was close to the vena cava, which was compressed and partially obliterated in a tract between the confluent of the left renal vein and the iliac biforcation. Even the mesenteric superior and the splenic veins were compressed by the mass. No evidence of liver metastasis was found.

The patient underwent ultrasound-guided aspiration of 1,300 cc of cystic fluid and biospsy of the solid vegetations. The dosage of oncomarkers in the fluid revealed a very high level of CEA (66,898 ng/mL) and CA. 19-9 (>10,000 UI/mL). Biopsy was not informative.

At laparotomy signs of portal hypertension were evident and a huge, smooth cystic tumour was found arising from the body and the tail of the pancreas (Figs. 2 and 3). A distal pancreatectomy with splenectomy was performed. The specimen was a cystic mass with a diameter of 16 cm, containing a large quantity of hemorrhagic material. The inner surface showed gelatinous tissue (Fig. 4).

Pathological examination showed mucinous cystoadenoma with associated invasive ductal carcinoma, with an ovarian-like stroma (Figs. 5 and 6) and strong positivity for progesterone and estrogen receptors as well as vimentin and actin. The neoplasm was well delimited by a fibrous capsule. The remaining pancreatic parenchyma surrounding the cystic was free of disease. No metastasis in 2 perisplenic and 3 peripancreatic lymphnodes were detected. The neo-

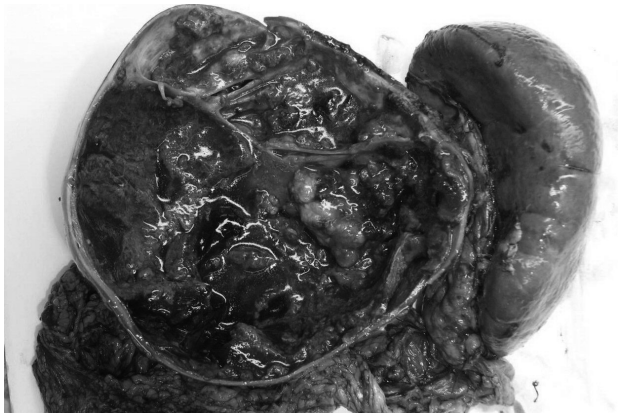

Fig. 4 - Surgical specimen.

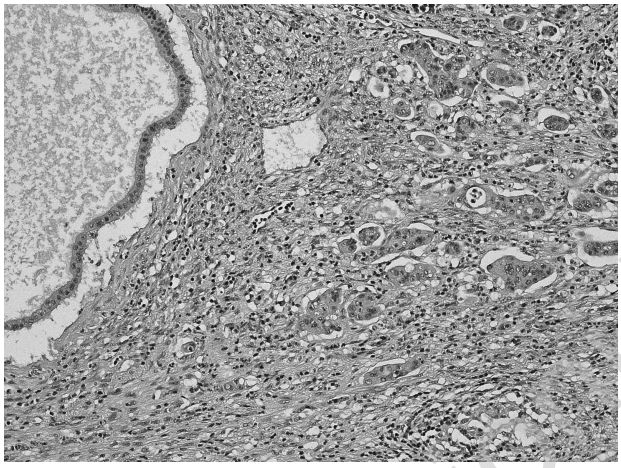

Fig. 5 - Histology. Cyst wall with numerous cavities filled with mucous. Small foci of invasive carcinoma are present (H&E, 2x).

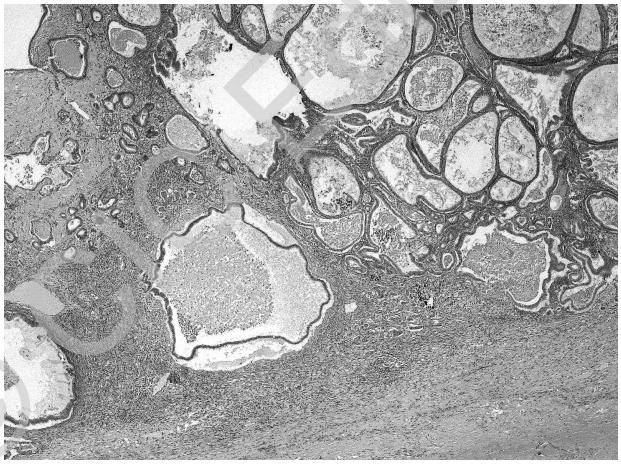

Fig. 6 - Histology. High power microphotograph showing the invasive component (H&E, 20x).

plasm was classified as pT1N0M0. The postoperative period was uneventful and the patient was discharged in the ninth day. She is currently alive and free of disease after a 6 months follow up.

Discussion

MCNs are defined as mucin-producing and septated cyst-forming epithelial neoplasia of the pancreas with a distinctive ovarian-type stroma. In 2004, the Consensus Conference of the International Association of Pancreatology in Sendai (Japan) (11,12) established that the histological presence of unique ovarian-like stroma was mandatory to diagnose MCN and was never found in other pancreatic neoplasms. The origin of ovarian stroma of the pancreas is still being debated (13). A stimulation of endodermal immature stroma by female hormones or primary yolk cell implantation in the pancreas has been suggested in literature (1) because buds of the genital tract and dorsal pancreas are adjacent to each other during embryogenesis. Moreover, embrional dorsal pancreas mainly gives rise to the pancreatic body and tail, and this could explain the predilection of MCNs for the distal pancreas (14). Usually solitary, the size of these tumors ranges between 5 and 35 cm with a thick fibrotic wall and without communication with the pancreatic ductal system (15). MCNs are rare, accounting for about 8% of surgically resected cystic lesions of the pancreas and, in most series, show a female to male ratio of 20 to 1 and a mean age at diagnosis of between 40 and 50 years (range 14-95 years) (1,16,17). The site of the neoplasm is in the body and tail of the pancreas in 95%-98% of cases (17,18).

Non invasive MCNs are categorized as MCNs low-grade, intermediate-grade and high-grade dysplasia. If there is a component of invasive carcinoma, the lesions are designated as MCNs with an associated invasive carcinoma. Consequently Zamboni et al. stated that terms such as mucinous adenocarcinoma not otherwise specified (NOS) or non invasive mucinous adenocarcinoma are no longer to be used (1). Usually patients with MCN with invasive carcinoma are 5-10 years older than those with non invasive MCN, suggesting that progression from non invasive curable neoplasm to invasive cancer occurs over a period of years.

MCNs with associated invasive adenocarcinoma follow the same pathways of local spread as invasive ductal adenocarcinoma. The first metastasis are tipically found in regional peripancreatic lymphnodes and liver. Staging follows the protocol of ductal carcinoma (1).

Histochemically MCTwas found to show positive tumor cells for progesterone receptors with absence of positive cells for estrogen receptors. Zamboni et al suggested that this may simply reflect a lower sensitivity of estrogen receptor antibody failing to reveal the biochemically detectable estrogen receptors. In fact, they reported that the nuclei were positive for progesterone receptors in 26 of 56 cases (48%) and for estrogen receptors in 12 cas-

es (22%) (19). In our case, positivity was found for both hormone receptors. MCTs of the pancreas can be sex hormone–dependent neoplasms. In literature, the high levels of female hormones during pregnancy are considered to be associated with the rapid growth and huge size of the lesions.

The majority of MCNs are slow growing and asymptomatic (20). When present the typical clinical appearance is characterized by epigastric heaviness and fullness (60%-90%) or by abdominal mass (30%-60%). Nausea, vomiting (20%-30%) and back pain (7%-40%) can also be present (1,17,21). In pregnancy the diagnosis may be is difficult since insidious symptoms and bodly changes may mask the true clinical condition.

Current imaging is not sufficiently accurate to allow for differentiation among multiple benign, premalignant, and malignant lesions (22). In fact the preoperative diagnosis is correct only in one-third of cases (2, 23). Nevertheless, multilocularity and the presence of papillary projections or mural nodules as well as a large size (>15 cm in diameter) or increasing size have been reported as signs of malignant MCN (1,3,23).

Several reports have addressed the diagnostic value of a cyst fluid analysis in differentiating cystic lesions of the pancreas (24, 25). In particular, CEA has been shown to be a useful marker for differentiating mucinous tumors from non-mucinous ones, while CA.19-9 is a less discriminating marker in the diagnosis of such tumors. High levels of CEA (>400 ng/ml) and CA.19-9 (>50,000 U/ml) in cystic fluid, as in our case, have a good specificity for differentiating pseudocysts from mucinous tumors but do not provide a reliable determination of malignant tumors (24).

Pregnancy has been reported to be complicated by pancreatic neoplasms, including cancer, papillary-cystic tumor, MCT, and insulinoma (26,27). This may be related to the theory that the pancreas is a sex steroid–dependent tissue (28). Among these neoplasms, large pancreatic MCT accompanying pregnancy are extremely rare. Up to now, there have been three report cases of pancreatic mucinous cystadenoma, , and 4 cases of pancreatic mucinous cystadenocarcinoma, associated with pregnancy (4-10). To the best of our knowledge our case is the eighth described in English literature.

With the exception of our case and the case desribed by Berindoague et al. (9), all other cases were diagnosed during pregnancy and in 5 patients surgery was performed during the second trimester of pregnancy due to the malignant potential of the lesion, its large size possibility of intrauterine growth restriction and symptoms, or tumour rupture, while in other two cases the surgery was performed only after delivery (4-10).

A pancreatic mass detected during pregnancy requires special consideration for management because of its tendency to rapid growth. There are several issues to be considered and the first is the timing of surgery. It has been suggested that the best time for surgery would be early in the second trimester when the risk of abortion is lowerand surgery is easier (29). A mass detected in the third trimester not suspicious of malignancy is best managed by waiting until delivery. Anyway careful and strictly monitoring is mandatory in all cases of cystic lesion of the pancreas during pregnancy. The second issue is fetal intrauterine growth restriction. In the case reported by Kato et al., the tumor increased in volume over 46 days and appeared to compress the fetus in the abdomen (4). The third issue is the risk of a tumor rupture due to the high estrogen levels during pregnancy or to labour (30). In a recent report, Naganuma described a ruptured mucinous cystic neoplasm with associated invasive carcinoma of the pancreatic head, presenting as acute abdomen during pregnancy. In this case after emergency cesarean section the patient underwent emergency pancreaticoduodenectomy (10). In our case, we were facilitated by the fact that the diagnosis and the hospital admission were made two weeks after labour and the patient was lucky enough because fetal intrauterine growth was not impaired and no rupture of the mass happened during labour.

The treatment of choice for pancreatic MCT is complete resection of the tumor (3). Even though enucleation is possible as alternative procedure for benign cystic neoplasm of the pancreas, the malignant potential of this tumour could not be ruled out and consequently this procedure could be inadequate (31). Spilling of the cystic contents should be avoided during the surgical procedure since this may lead to the complication of *pseudomyxoma peritonei* (8).

Conclusion

We report the eighth case of MCN of the literature, and the fifth one of MCT associated with invasive adenocarcinoma of the pancreas, developing during pregnancy. This pathological entity should always be kept in mind in patients that present hepigastric mass during or soon after pregnancy. Aggressive approach is mandatory due to malignant potential of the lesion and to avoid complications.

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