Pancreatic tumor in a pregnant woman: A rare case report

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Summary

We have analyzed a case of pancreatic carcinoma in a pregnant woman, 37 years old, in the second trimester of the pregnancy. She had a positive family history of digestive tract carcinoma. The delivery ended surgically and hysterectomy was performed at the same time.

Key words: Pancreatic tumor; Pregnancy; Delivery.

Introduction

Pancreatic carcinoma is the fifth largest cause of death due to cancer in women and the fourth in men. It is a fast, progressive disease, with an average survival period of only six months after the diagnosis. Expected 5-year survival rate is less than 3%. So far, only surgical resection gives the possibility of long-term survival in patients with pancreatic carcinoma. Unfortunately, the percentage of resectability in these patients is only 15%-25%. In the last ten years, due to the advancement in surgical techniques, postoperative morbidity and mortality have been significantly reduced.

The increased incidence of pancreatic carcinoma in the last 70 years can be partially explained by improvement in diagnostic procedures, decreased number of people who die without an established diagnosis and increased population age. The best known among the prognosis complexes is epidermal growth factor receptor (EGFR) with its ligands: epidermal growth factor (EGF - cannot be detected in a normal pancreas), transformed growth factor α (TGF-α), amphyregulin, betacellulin and epiregulin. Increased EGFR expression of one or more of its ligands is a bad prognostic parameter and is associated with increased metastatic potential, tumor invasivity and shorter survival.

There are three more receptors closely connected to EGFR: HER 2, HER3 and HER4 with their own ligands. For example, it is well-known that betacellulin bonds to HER4, specifically producing Langerhans island β cells. The increased expression of HER2 receptors in pancreatic cancer does not seem to be related to tumor progression but to better differentiated phenotype, while the increased expression of HER3 receptors in carcinoma is associated with tumor progression and a shorter survival period.

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Hepatocyte growth factor and MET receptor

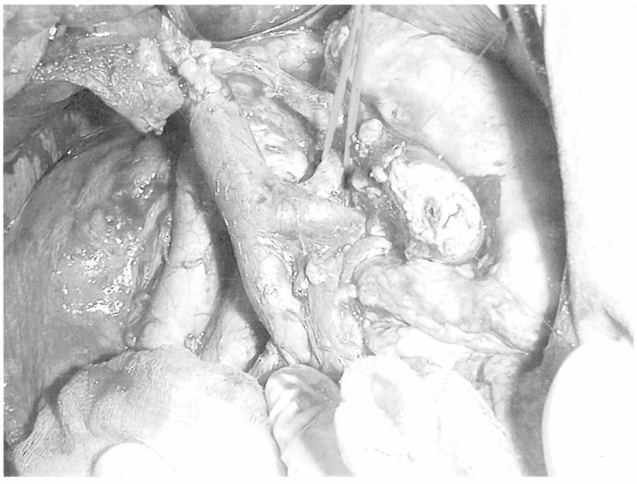
In pancreatic carcinoma there is a ten times higher concentration of hepatocyte growth factor.

Transformed growth factor β consists of a group of regulatory polypeptides which include three isoforms: TGF-β1, TGF-β2 and TGF-β3. It acts as a growth inhibitor for most epithelial cells. In pancreatic cancer there is a multifold increase of the expression of these isoforms. It is supposed that by the loss of response to the inhibitory action of TGF-β isoforms, the growth of tumor cells is enabled. There is also an increased expression of fibroblast growth factors and their receptors in pancreatic carcinoma. The most common genetic disturbance in pancreatic carcinoma is K-ras mutation. The mutation at codon 12 of the K-ras oncogene is present in at least 75% of cases of progressive ductal adeno carcinoma of the pancreas. A dominant change in pancreas carcinoma, similar to colorectal carcinoma, is a change of guanine into adenine (G into A) in contrast to a change of guanine into timine (G into T) with lung carcinoma, which points to different chemical instigators. In endocrine pancreatic tumors K-ras mutations were not suppressor genes. The mutation of the p53 tumor suppressor gene is probably the most common genetic change in human carcinoma. The heterogeneous spectrum of p53 mutations suggests that these mutations can appear not only as a consequence of exposure to a certain chemical mutagen, but also because of endogenous mutagenesis. Other tumor suppressor genes, that can be included in the pathogenesis of pancreatic tumors, are p16, SMAD 4 and others. Vein thrombosis appears frequently in pancreas carcinoma and is provoked by the creation of thrombin by the tumor. Transmembrane cell receptor (TF cell surface tissue factor), a main initiator of coagulation in humans, is also included in this process.

Diagnostic application

The diagnosis of pancreatic carcinoma has become easier with the appearance of ultrasound, computed

Fig. 1



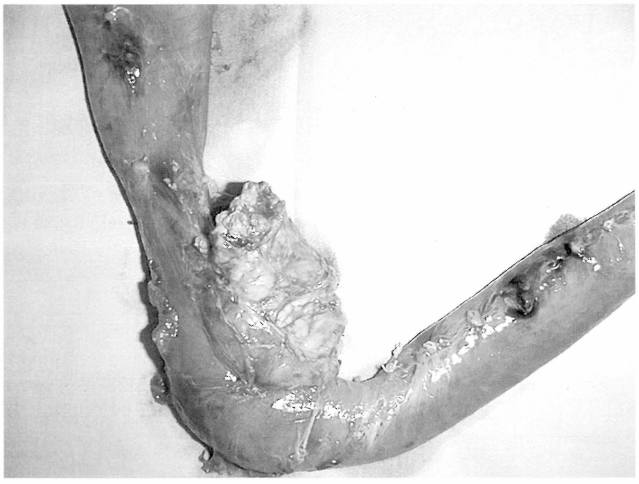


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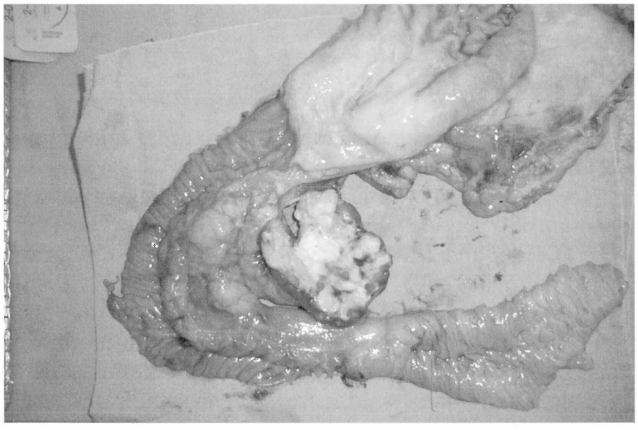
Fig. 3



Figures 1-3 – Pancreatic cancer intraoperatively and postoperatively.

tomography (CT) and magnetic resonance imaging (MRI). The definitive diagnosis in many cases however demands cytodiagnostics. Knowledge of molecular biology enables the application of biochemical and cytological analyses of clear pancreatic juice and smears, using endoscope retrograde holangiography, percutaneaus biopsy, serum and stool analysis. The two most common antigens produced by pancreatic carcinoma are Ca 19-9 and DU-PAN-2. Ca 19-9 is produced in nearly 80% of the cases with comparable serological values and DU-PAN-2 has bad serological expression. Thus, using them together has the largest diagnostic value. Ca 19-9 serological increase is also used as an index of resectability. The mutations of oncogenes and tumor suppression genes can be detected by simple but sensitive PCR (polymerase chain reaction) analysis. K-ras mutations can be detected not only in body fluids but also in stool samples. It was recently published that tumor cells carrying K-ras mutations can be found in patient's peripheral blood even in cases without clinically observed metastases.

Case Report

We analyzed a case of pancreatic carcinoma in a pregnant woman. Even with the increased incidence of malignancies in our country the diagnosis of pancreatic carcinoma during pregnancy is very rare.

The clinical appearance is pain in the head zones, frequent and fatty stools, and then constipation. Laboratory analyses of billirubin, transaminase, exclusion of hepatitis, serum amylase lipases and sugar level monitoring were performed.

After the differential diagnosis, by using laboratory and ultrasound examinations, we suspected a form of carcinoma that is rare in pregnant patients.

Following artificial maturation and surgical delivery the patient was subjected to surgical therapy immediately after delivery.

There was a disturbance in laboratory parameters in terms of a possible hepatitis diagnosis and the incidence of diabetes. The patient was an older primipara, 37 years old. She had a positive family history for digestive tract carcinoma. She was in the second trimester of the pregnancy.

Clinical symptoms were primarily pain in the head zones, the incidence of fatty and frequent stools, and then constipation. The patient had a weight loss but it was not significant, i.e. 0.5 kg in ten days.

After the exclusion of hepatitis, analyzing the Ca 19-9 level and abdominal ultrasonographic examination, pancreas carcinoma was suspected.

During the examination, the condition of the fetus and fetoplacental unit did not suggest signs of insufficiency. Doppler flow results were within referent values.

Because of the mother's vital signs, and in association with the surgical team and the with patient's consent, we applied the procedure of intensive fetal maturation by injecting 12 mg betamethasone and 0.25 g cephalexine, under ultrasound control, into the glutial part of the fetus.

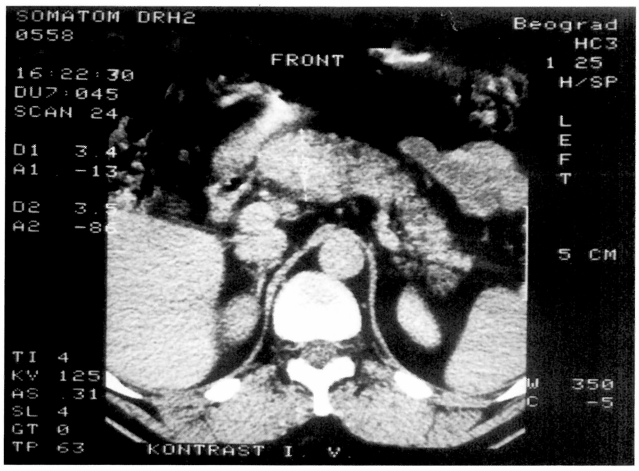


Fig. 4

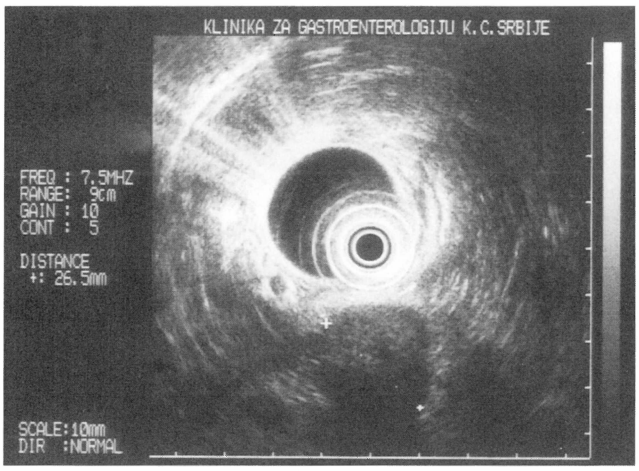


Fig. 5

Figure 4 – Computed tomography.
Figure 5 – RCP endoscopic retrograde cholangiopancreatography.

After preoperative preparation, the delivery ended surgically. Subsequently hysterectomy was performed considering the danger of the mother's lowered immunity and the necessity to proceed with surgical intervention because of the mother's vital indications.

The newborn, a female with a body weight 1,450 g, was transported to the institute for preterm babies, where it was treated by low doses of intranasal oxygen. After birth, surfactant was applied with short-term intubations during the first 48 hours. There were no signs of intracranial hemorrhage or infection though the child was treated by prophylactic antibiotics.

The surgical team started to remove the pancreas, preserving the gastric veins and arteries, and performed terminalileal anastomosis.

Postoperative recovery was regular but long. The patient's lactation was stopped by administration of bromergone, in 5 mg doses from the third to the tenth postoperative day.

After histopathological analysis, the diagnosis of pancreatic Aden carcinoma was established, and the preoperative hypothesis about a larger malignant potential was confirmed. The patient was referred to cytotherapy.

Discussion

Pancreatic tumors are more common in the male population. The literature data about the incidence of pancreatic tumors in pregnant women are rare.

The fact that the patient did not belong to a risk group implies more precaution with symptoms that seem harmless at first glance. Back pain can be interpreted as sciatica or preterm delivery. Also, increased transaminases are associated with the possibility of some form of hepatitis. The changes in stools are more common in organism intoxication. The increased levels of glucose in gravid patients are the primary association of gestative diabetes, especially in older pregnant patients. Our patient was a non-smoker and did not consume fatty food but there was a positive family history of gastrointestinal tract tumors. Moreover, the decision to end the pregnancy earlier by artificial maturation because of the mother's vital parameters enabled us to save the fetus.

The mode of delivery was imposed by the fetus and the fact that it was necessary to perform a surgical procedure as soon as possible to avoid a prolonged vaginal delivery in a primipara with an inadequate Bishop score and preterm pregnancy, and to avoid additional physical and mental stress for the mother. Also, by surgical delivery, intracranial hemorrhage in the newborn was prevented. Even though vaginal delivery seemed more efficient in the earlier stages of delivery because of fetal maturation, in terms of fetal adrenalin activation and consequently of surfactant increases in the fetal alveoli, we decided to end the delivery by surgery even with a Bishop score of 0. Also, when preterm vaginal delivery starts, the literature data show that there is a larger number of intracranial hemorrhages in immature fragile fetal head blood vessels even though blood vessel vulnerability is decreased by administration of corticosteroids.

As continuation of the surgery was necessary and because the surgery was performed on the digestive tract, we decided to perform a hysterectomy to decrease all potential risk factors of the mother's lowered immunity and to enable an easier postoperative recovery because of uterus vulnerability and the possibility of infections, and also because of lower puerperal immunity and changes in the uterus.

Easier and faster recovery of grave patients is enabled by canceling lactation even though the psychological aspect of it is also lost.

Conclusion

Although rare, not only in the female population but also in pregnant women, the pathology leads us to the necessity of a quick and aggressive diagnosis in all cases. The methods of artificial fetal lung maturation enable us to end pregnancy earlier but successfully in conditions of vital importance for the mother. The postoperative course in patients with malignant potential declines during puerperium by stopping lactation and thus eliminating the

uterus and ovaries as *locus minoris* for the incidence of infection, sepsis and lower immunity. Immediately after the histopathological analysis, cytological and radiological therapy was established. Even though this is a recent case of our new pathology, the patient is still alive but under close monitoring and so far without substitutional gynecological therapy.

References

[1] American Cancer Society: Cancer Facts and Figures, 1980
[2] Brooks J.R., Culebras J.M.: "Cancer pancreas, palliative operation, whipple procedure or total pancreatomy". *Am. J. Surg.,* 1976, *131,* 516.
[3] Wynder W.L., Mabuchi K., Maruchi N. *et al.*: "Epidemiology and carcinoma of the pancreas". *JNCI,* 1993, *50,* 645.
[4] Howard J., Jordan G.: "Surgical Disease of the Pancreas". Philadelphia, J.B. Lippincot, 1980.
[5] Nielsen O.H., Andreasson B.: "Pregnancy in pancreatic disease". *Scand. J. Gastroenterolog.,* 1993, *18,* 735.
[6] Lankisch P.G., Koop H., Otto J. *et al.*: "Specificity of increase amilase and creatinin clearance ratio in acute pancreatitis". *Digestion,* 1997, *16,* 160.
[7] Levitt M.D., Jhohnson S.G.: "Is the Cam/Cex ratio of value for the diagnostis of pancreatitis". *Gastroenterology,* 1989, *75,* 118.
[8] Andres R.L.: "Effects of therapeutic, diagnostic and environmental agents and exposure to social and illicit drugs". Maternal-fetal Medicine, 5th ed., W. B. Saunders, 2000, 281.
[9] King A.: "Immunobiology of placentation: implications for fetal growth and development". Textbook of Neonatology, 3rd ed., Churchill Livingstone, 1999, 235.
[10] Weiner C.P., Buhimschi C.: "Drugs for pregnant and lactating women". Churchill Livingstone, 2004.

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