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Pancreatic neuroendocrine carcinoma in a pregnant woman: A case report and review of the literature

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Abstract

BACKGROUND

Portal venous thromboembolism caused by malignant pancreatic neuroendocrine tumor metastasis, as the initial presentation of portal hypertension and upper gastrointestinal bleeding, is a rare entity. To our knowledge, there are no reports of this entity in pregnant women. We describe a case of pancreatic neuroendocrine carcinoma during pregnancy with hematemesis and hematochezia as the initial presentation and review the literature to analyze the demographic, clinical, and pathological features to provide a reference for clinical diagnosis and treatment.

CASE SUMMARY

A 40-year-old woman presented with hematemesis and hematochezia at 26-wk gestation; she had no other remarkable medical history. The physical examination revealed normal vital signs, an anemic appearance, and lower abdominal distension. Abdominal color Doppler ultrasonography showed portal vein thrombosis, splenomegaly, intrauterine pregnancy, and intrauterine fetal death. Esophagogastroduodenoscopy revealed esophageal and gastric varicose veins and portal hypertensive gastropathy. Contrast-enhanced computed tomography demonstrated multiple emboli formation in the portal and splenic veins, multiple round shadows in the liver with a slightly lower density, portal vein broadening, varicose veins in the lower esophagus and gastric fundus, splenomegaly, bilateral pleural effusion, ascites and pelvic effusion, broadening of the common bile duct, and increased uterine volume. According to the results of Positron emission tomography-computed tomography and immunohistochemical staining, the final diagnoses were that the primary lesion was a pancreatic neuroendocrine tumor and that there were secondary intrahepatic metastases and venous cancer thro-

Checklist (2016).

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mbogenesis.

CONCLUSION

Upper gastrointestinal bleeding in a pregnant woman may be caused by portal hypertension due to a malignant pancreatic neuroendocrine tumor.

Key Words: Pregnancy; Portal venous thromboembolism; Pancreatic neuroendocrine carcinoma; Portal hypertension; Gastrointestinal bleeding; Case report

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Core Tip: Upper gastrointestinal bleeding caused by portal hypertension is a rare form of advanced pancreatic neuroendocrine tumor. Our patient presented with hematemesis and hematochezia at 26-wk gestation, but no other significant medical history. Positron emission tomography-computed tomography revealed that lesions in the liver were found to be pancreatic neuroendocrine carcinoma during pregnancy. This case demonstrates that upper gastrointestinal bleeding as the initial presentation should be suspected among pregnant patients at high risk for malignancies.

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INTRODUCTION

Neuroendocrine neoplasms (NENs) are a group of heterogeneous tumors originating from peptide neuroendocrine neurons and neuroendocrine cells, commonly occurring in different parts of the body, including the lung, thymus, pancreas, and gastrointestinal tract[1]. The incidence of pancreatic NENs (pNENs) is 0.32/100000 person-years. According to the World Health Organization classification criteria for digestive system tumors in 2019, the gastrointestinal tract/hepatobiliary/pancreatic NEN was divided into well differentiated neuroendocrine tumor (NET) and poorly differentiated neuroendocrine carcinoma (NEC). Malignant pNENs account for approximately 1% of pancreatic malignancies, with a peak age of 40-69 years and a male-to-female ratio of 1.33:1[2]. pNEN in pregnancy is a very rare condition and its diagnosis and treatment can be very challenging. Here, we report a case of pancreatic NEC (pNEC) during pregnancy with upper gastrointestinal bleeding as the initial presentation and review the related literature to analyze the demographic, clinical, and pathological features to provide a reference for clinical diagnosis and treatment.

CASE PRESENTATION

Chief complaints

A 40-year-old woman at 26-wk gestation was admitted to the hospital for hematemesis, hematochezia, and abdominal pain for 10 h.

History of present illness

Abdominal color Doppler ultrasonography showed portal vein thrombosis, splenomegaly, intrauterine pregnancy, and intrauterine fetal death.

History of past illness

The patient had no significant past medical history.

Personal and family history

The patient had no history of smoking or alcohol consumption. She had no relevant

family history.

Physical examination

The physical examination revealed that the patient had normal vital signs, a body weight of 56 kg, a height of 1.58 m, a body mass index of 22.4 kg/m², an anemic appearance, and lower abdominal distension, and had no abdominal shiftiness sound.

Laboratory examinations

The laboratory examination was otherwise unremarkable. The laboratory assessment included an initial blood test of the complete blood count (hemoglobin level, 76 g/L), liver test (albumin level, 29.9 g/L), and tumor markers (alpha-fetoprotein level, 179.60 ng/mL; cancer antigen 125 level, 209.40 U/mL; and cancer antigen 199 level, 168.20 U/mL). Viral hepatitis markers were negative. Glucose and serum insulin levels were normal.

Imaging examinations

Esophagogastroduodenoscopy revealed esophageal and gastric varicose veins and portal hypertensive gastropathy (Figure 1). Contrast-enhanced computed tomography (CT) demonstrated multiple emboli formation in the portal vein and splenic vein, multiple round shadows in the liver with a slightly lower density (metastatic tumors were mostly considered), portal vein broadening, varicose veins in the lower esophagus and gastric fundus, splenomegaly, bilateral pleural effusion, ascites and pelvic effusion, broadening of the common bile duct, and increased uterine volume. Ultrasound-guided fine-needle aspiration biopsy of the liver tumor was performed. Histologically, the tumor consisted of heterogeneous cells arranged in nests, with a small cell extraction volume, short spindle or polygonal, unclear cell boundary, eosinophilic cytoplasm, increased nucleoplasmic ratio, and varying degrees of nuclear atypia. Immunohistochemical staining revealed that the tumor cells were positive for CKp, synaptophysin (Syn), chromogranin A (CgA), CD10, CD56, CDX-2, CEA, and Ki67 (40%+) (Figure 2). To identify the primary lesion, ¹⁸F-fluorodeoxyglucose Positron emission tomography/computed tomography (¹⁸F-FDG-PET-CT) was performed and showed multiple metabolic elevations in the pancreatic tail area, intrahepatic portal vein, and adjacent mesenteric and splenic veins. Considering the pathological tendency, it was considered that there was a high possibility of primary lesions of pNEC, secondary intrahepatic metastasis, venous cancer thrombogenesis, and corresponding varicose veins. No other metastatic lesions were found (Figure 3).

FINAL DIAGNOSIS

These aforementioned findings supported a diagnosis of pNEC (T2N0M2, G3) in pregnancy, secondary malignant tumor of the liver, and multiple venous thrombi.

TREATMENT

Subsequently, the patient was transferred to other hospitals for further treatment. The patient underwent transcatheter arterial chemo-embolization three times and radiofrequency ablation one time and was administered Sandostatin (octreotide acetate microsphere, 30 mg) once a month, without systemic chemotherapy or targeted drugs.

OUTCOME AND FOLLOW-UP

In February 2020, abdominal contrast-enhanced CT demonstrated the following: (1) Multiple intrahepatic tumors were present. Compared with the previous image (November 2019), the lesion volume of the hepatic hilum increased, abdominal exudation and liver injury reduced, necrosis appeared in some lesions, and little change was seen in the rest of the lesions; (2) The volume of emboli in the portal vein and inferior vena cava was increased, and multiple collateral circulations formed around the portal vein. Varicose veins were also present in the lower esophagus and gastric fundus; and (3) Splenomegaly was present (Figure 4A). In June 2020, abdominal contrast-enhanced CT showed the following: (1) Multiple tumors in the liver were accompanied by accumulation of lipiodol, and the accumulation increased

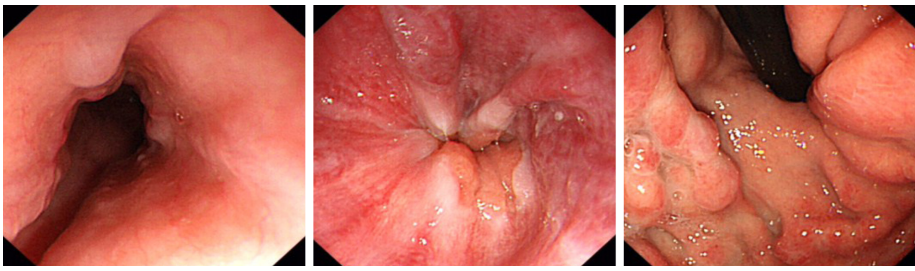


Figure 1 Esophagogastroduodenoscopy showing esophageal and gastric varicose veins.

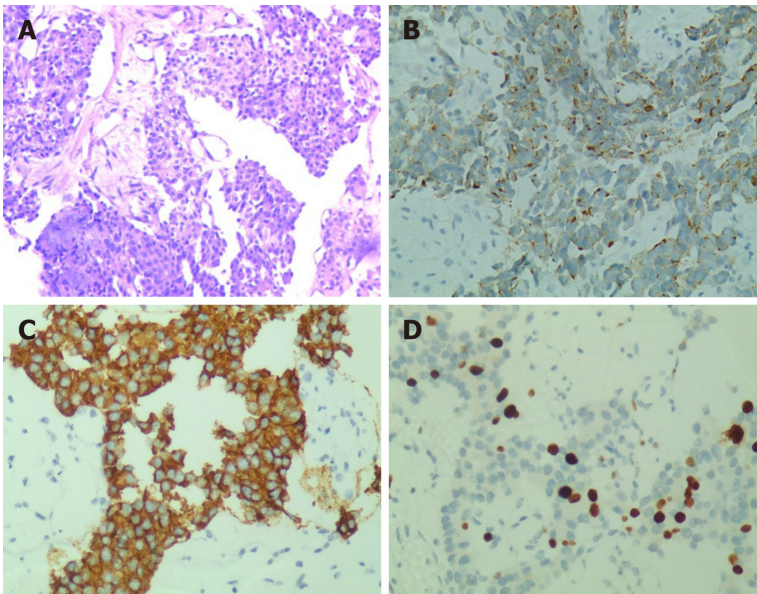


Figure 2 Ultrasound-guided fine-needle aspiration biopsy of the liver tumor. A: Hematoxylin and eosin staining ($\times 200$); B-D: Immunohistochemical staining for (B) Chromogranin A (+), (C) Synaptophysin (+), and (D) Ki67 (40%+).

in the lesion compared with that in the previous lesion (February 2020). The lesion scope of the pancreatic tail was reduced. Multiple collateral circulations formed around the portal vein. Varicose veins remained present in the lower esophagus and gastric fundus; and (2) Splenomegaly was still present (Figure 4B).

Even though the patient's weight was about 10 kg less than before, she was physically active and could take care of herself.

DISCUSSION

In a review of published literature in China and abroad from 1939 to 2019, 41 cases of pNENs during pregnancy were collected, among which 29 were insulinomas in patients with an average age of 29 years[3-28] (Table 1). In this study, the clinical manifestations and pathological characteristics of pNENs during gestation are summarized and analyzed. Pregnancy-associated pNENs, diagnosed during pregnancy and in the first year postpartum, may vary in type and differentiation, leading to atypical symptoms and signs and various clinical manifestations. This is an important reason why physicians and patients ignore and delay diagnosis. Functional pNENs have been observed at various stages of pregnancy, and the most common form of insulinoma is associated with hypoglycemia, including effects on the central nervous system, such as headaches, confusion, visual and behavioral abnormalities, or hypoglycemia that causes excessive catecholamine release, *e.g.*, perspiration, tremor, and palpitations. A functional pNEN is easy to be misdiagnosed clinically because it is confused with pregnancy-associated uncomfortable symptoms[29]. Symptoms of nonfunctional pNENs appear when they have local spread or distant metastases. It is challenging to perform paraclinical tests on patients with nonfunctional pNENs. In

Table 1 Summary of pancreatic neuroendocrine neoplasms in pregnancy (2000-2019)

Ref.	Patient age	Onset of symptoms	Symptoms	Management	Maternal outcomes	Fatal outcomes
Fredericks <i>et al</i> [19]	35-yr-old	Three weeks post-partum	Neuroglycopenic symptoms	Laparotomy the tumor	No symptoms after removal	Live born
Takacs <i>et al</i> [20]	28-yr-old	At 6-wk gestation	Difficult morning arousability	Exploratory laparotomy	No residual symptoms	Cesarean delivery Live born
Lowy and Chisholm[23]	36-yr-old	Twelve hours post-partum	Severe hypoglycaemia	Excision of the lesion	No symptoms after removal	Live born
Diaz <i>et al</i> [24]	35-yr-old	Three months Post-partum	Loss of consciousness	Exploratory laparotomy	No residual symptoms	Live born
Diaz <i>et al</i> [24]	35-yr-old	On the 26 th postpartum day	Confusion, dysarthria, and quadriplegia	Enucleation of an 8-mm tumor	No symptoms after removal	Live born
Diaz <i>et al</i> [24]	22-yr-old	At 2-mo gestation	Loss of consciousness	Laparoscopic distal pancreatectomy Post-partum	No residual symptoms	Natural labor Live born
Christiansen and Vestergaard[25]	29-yr-old	At 38-mo gestation	Slurred speech, weakness	Pancreaticoduodenectomy and cholecystectomy Post-partum	No symptoms after removal	Natural labor Live born
Rodrigues Queiróz <i>et al</i> [26]	21-yr-old	Eight days post-partum	Four limbs weakness, difficult walking	Pancreatectomy	No residual symptoms	Live born
Mannelli <i>et al</i> [27]	29-yr-old	At 17 wk gestation	Severe hypoglycemia	Started therapy with everolimus	Died 3 yr after delivery	Cesarean delivery Live born
Tomazic <i>et al</i> [28]	36-yr-old	In the second trimester of pregnancy	Hypoglycemia associated with neuroglycopenic symptoms	Distal pancreatectomy at 21 wk gestation	No symptoms after removal	Nature labor Live born

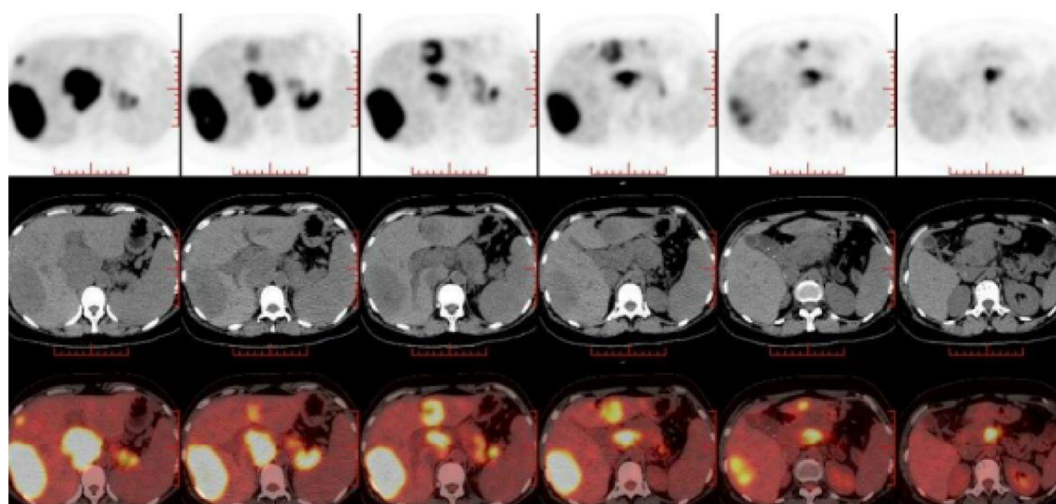


Figure 3 ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography revealing a high possibility of a primary lesion of pancreatic neuroendocrine carcinoma, secondary intrahepatic metastasis, venous cancer thrombogenesis, and corresponding varicose veins.

particular, invasive exploration (imaging, endoscopy, *etc.*) may be harmful to the fetus. Clinical diagnosis of pNENs in pregnancy is difficult because of the lack of specific clinical symptoms and CT/magnetic resonance imaging (MRI) findings[30].

Metastasis of a malignant pNEN to the liver in pregnant women is a rare entity, and little is known about the risk factors for its pathogenesis. The risk of cancer has been reported to increase with age, and the distribution of maternal age affects the

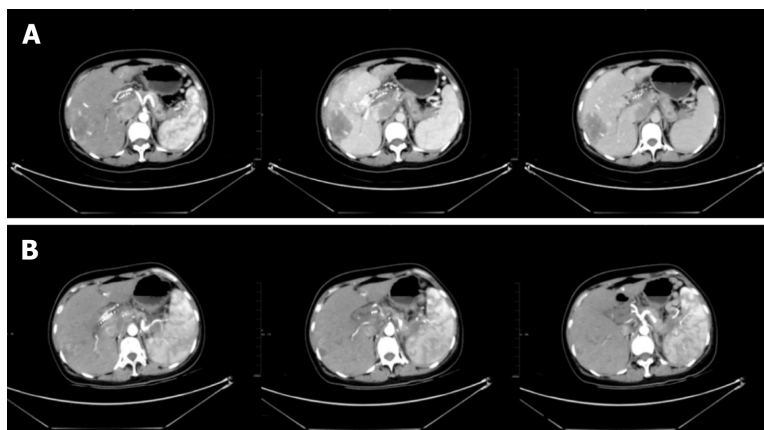


Figure 4 Imaging findings. A: Abdominal enhanced computed tomography (CT) in February 2020 demonstrated the following: (1) The presence of multiple intrahepatic tumors. Compared with the previous image (November 2019), the lesion volume of the hepatic hilar was increased, abdominal exudation and liver injury were improved, necrosis appeared in some lesions, and little change was seen in the remaining lesions; and (2) the volume of emboli in the portal vein and inferior vena cava was increased, and varicose veins were present in the lower esophagus and gastric fundus; B: Abdominal contrast-enhanced CT in June 2020 revealed multiple tumors in the liver accompanied by the accumulation of lipiodol, and increased accumulation of lipiodol in the lesion compared with the previous lesion (February 2020). The lesion scope of the pancreatic tail was reduced.

incidence of pregnancy-associated cancers. The mechanisms and hormone allocation that lead to changes in maternal cancer risk are not fully understood. According to a wide range of clinical medical data, increasingly more women develop cancer during pregnancy due to delay in the age of conception. According to statistics, the incidence of malignant tumors in pregnant women during pregnancy is about 0.07% to 0.1%. Risk factors specific to pregnant women may include high estrogen levels, long-term fat intake, reduced physical activity, high blood pressure, and pre-existing chronic kidney disease; genetic and environmental sources of pregnancy-related cancers are likely to predate pregnancy. Moreover, hormones and growth factors necessary for fetal growth may accelerate tumor growth, such as estrogen, insulin-like growth factor I, and angiogenic factors, which may lead to maternal cancer and deserve further study. In addition, pregnancy is a pro-angiogenic state, and the placenta and angiogenesis required by pregnancy (placental growth factor and vascular endothelial growth factor, *etc.*) contribute to the occurrence or growth of tumors[31]. During pregnancy, there is a higher risk of tumor complications, such as thromboembolic events and septicemia; however, physiological changes during pregnancy may delay the diagnosis of tumors and have an adverse effect on pregnancy outcomes.

CT, MRI, PET, transabdominal ultrasonography, gastrointestinal endoscopy, and endoscopic ultrasonography can be used to evaluate tumor staging and establish the diagnosis. The detection of pNENs by CT, MRI[32,33], and other imaging investigations is affected by tumor size, and establishing the diagnosis of pNENs decreases significantly when the tumor is small (< 2 cm). PET-CT seems to be useful in identifying the primary tumor site and assessing the degree of metastases at distant sites. The sensitivity of gallium 68Ga-PET-CT is higher than that of 18F-FDG-PET-CT in determining staging of pNENs[34,35]. However, in pregnant women with pNENs, such tests are considered only after weighing the advantages and disadvantages.

Serological examination of pNENs during pregnancy can be performed, and serum CgA is the most widely used and valuable biomarker for diagnosis and follow-up of NENs[36], which can be used as an adjunctive diagnosis; other tumor biomarkers include neuron-specific enolase (NSE), Syn, and 5-hydroxyindoleacetic acid, and specific immunohistochemical staining markers of CgA, Syn, and NSE are the gold standard for identifying NENs.

Unlike conventional pNENs, cases of pNENs in pregnancy are scarce, and there is no standard therapeutic treatment. However, the therapy for pNENs is primarily surgical. Treatment requires a multidisciplinary approach that results in an appropriate, balanced, and optimal treatment plan, covering oncology, gynecology, surgery, psychology, anesthesiology, neonatology, and that considers ethical, family, and other relevant factors. Foreign scholars generally seem to agree that the treatment of pregnant women is the priority, followed by ensuring the healthy development of the fetus[37]. The basic criteria for the treatment decision are imaging identification of the tumor location, characteristics of the tumor behavior, severity of symptoms, duration of pregnancy, and preference of the family. When the tumor is undetected,

conservative treatment is warranted and surgical procedures are postponed as long as possible. This buys time for the fetus to develop more, and since pNENs grow over time, the site can be clearly diagnosed and then treated by therapeutic excision[38].

Chemotherapy is the first choice for advanced metastatic tumors, and the apparent aim is to prolong the life of the mother until safe delivery[39]. Chemotherapy provides a palliative care option for pregnant women and postpartum patients if the fetus is of appropriate age. The risks to the fetus must be understood before chemotherapy is performed, and a range of moral, religious, ethical, and legal considerations must be taken into account. The extent to which the fetus receives chemotherapy and its effects depend on the progress of the pregnancy; chemotherapy must not be administered at 33 wk before birth or 3 wk after birth. The usual treatment regimen for pancreatic NETs is the use of antimetabolites (such as 5-fluorouracil) and some alkylating agents (such as streptozotocin)[40], with minimal effect on the fetus. The fetal toxicity of multi-drug chemotherapy increased from 17% to 25% compared with monotherapy[41]. Molecular targeted therapies, such as mammalian target of rapamycin pathway inhibitors (*e.g.*, iverimus) or antiangiogenic drugs (*e.g.*, sunitinib or other isomers), have not been adequately studied to provide information on fetal side effects[42-44]. For metastatic cases of pNECs during pregnancy, treatment is less likely. Surgical resection is the first treatment plan, followed by transcranial arterial chemoembolization, systemic chemotherapy, intratumoral ethanol injection, and radiofrequency ablation for liver metastasis[45]. Surgical treatment is still an option, but usually after birth or, if necessary, as late as possible after the fetus has reached the appropriate age (28 wk). The prognosis of pregnancy-associated pNENS differs depending on the pathological type and stage.

CONCLUSION

In conclusion, the primary lesion of pNEC during pregnancy in this case was relatively hidden, but multiple distant metastases of the liver, portal vein, mesenteric vein, and splenic vein occurred. Additionally, acute upper gastrointestinal hemorrhage was the initial presentation, which is relatively rare. In pregnant women with pNECs, a special patient group, physicians should not only focus on the patient's own disease but also consider the safety of the fetus, family, ethics, law, and other factors. Moreover, there is no unified diagnosis and treatment standard in China and abroad. Such patients require a multidisciplinary team for comprehensive clinical management and individualized treatment based on each patient's condition and the development of the fetus.

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