Effective control of postoperative recurrence of pregnancy-related gastric cancer using anti-PD-1 as a monotherapy

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Case Report

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Abstract

**Background:** Pregnancy related gastric cancer is characterised by refractory nature and poor prognosis, few gastric cancer cases during pregnancy achieved acceptable outcomes by using anti-PD-1 as a monotherapy.

**Case presentation:** A 32-year-old female patient was admitted to the emergency department of obstetrics and gynaecology department, and eventually diagnosed with gastric cancer. Radical surgery for gastric cancer was conducted after termination of pregnancy. One year postoperative follow-up exerted tumour recurrence, this patient has achieved promising results after receiving anti-PD-1 as a monotherapy.

**Conclusions:** Some specific pregnancy related gastric cancer patients may benefit significantly from immunotherapy.

**Background**

The diagnosis and treatment of gastric cancer during pregnancy is quite challenging, which unavoidably presents patients with the conflicting choices of individualized treatment and continued childbirth. This group of gastric cancer patients is characterised by refractory nature and dismal prognosis[1–3].

As for the treatment options, the application of immunotherapy is still controversial. Only some particular gastric cancer patients have achieved promising results after receiving anti-PD-1 therapy. There are very few gastric cancer cases during pregnancy who achieved satisfactory outcomes by using immunotherapy alone[4].

We report a case of a patient with gastric cancer during pregnancy who underwent radical gastric cancer surgery after elective induction of labour, yet postoperative tumour recurrence occurred, nevertheless, the patient refused chemotherapy and was treated with anti-PD-1 therapy alone, Intriguingly, the recurrent lesion was found to have continued to shrink during subsequent follow-up. The aim of this study is to provide experience and protocols for the comprehensive treatment of patients with gastric cancer during pregnancy.

A case of a pregnancy related gastric cancer who achieved promising results with immunotherapy alone will be reported. The study involving human participant was reviewed and approved by the Research Ethics Committee of Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University and was carried out in accordance with the ethical standards of the World Medical Association's Declaration of Helsinki. The patient provided written informed consent.

**Case presentation**

A 32-year-old female patient was admitted to the emergency department of obstetrics and gynaecology department, Ren Ji Hospital, Shanghai Jiao Tong University (Shanghai, China) with an emergency
admission of 11 hours for haematemesis with epigastric pain at 21 + 4 weeks of pregnancy on August 10, 2018. The patient had regular menstruation, age of menarche is 12 years old, menstrual cycle: 5–7/30, moderate volume and no dysmenorrhea. Fertility history: 0-0-0-0. LMP: 2018-03-18, EDC: 2018-12-30. Early pregnancy ultrasound verified gestational weeks, 4 months of menopause + felt fetal movement. The patient experienced severe vomiting on May 10, 2018 with pink foam in the vomitus and no concomitant symptoms such as abdominal pain, diarrhoea or melena. The patient regarded it was morning sickness and did not pay enough attention to it. Despite that, the vomiting gradually deteriorating until the patient was unable to eat normally. On August 1, 2018, she was presented to one of the Maternal and Child Health Hospital and was later recommended to be referred to Renji Hospital. The patient had no family history about cancer, nor did she have a history of smoking, alcohol drinking, or toxic environment exposure. Past history: In vitro fertilization-embryo transfer (IVF-ET)

Physical examination: Vital signs were stable, with a mild anaemic appearance, a mid to lower abdominal bulge and mild epigastric pain. The patient was admitted with black vomitus. Abdominal circumference: 94 cm, fundal height: 30 cm, no contractions, fetal heart rate: 149 bpm.

Auxiliary examination: Emergency gynaecological ultrasound: singleton cephalic position, fetal heart rate and fetal movement: visible, growth meridian: 51-188-158-33

Emergency ancillary tests: Hb: 95g/L; gastric fluid occult blood: positive, faecal occult blood: negative; AFP: 90.20ng/mL; CA 724: 172.10U/ml, CYFRA(21 − 1): 11.48ng/ml; CA242: 23.5U/ml. Upper-Abdomen Enhanced MRI: Space-occupying lesion of the gastric sinus, suspicious lymph node enlargement on the lateral side of the greater curvature of the gastric sinus, scan of the pregnant uterus (Fig. 1a -c). Electron fibroptic gastroscopy: Large ulcerated lesion of the gastric sinus, involving the four walls and the gastric angle, and the lesser curvature of the gastric body (Fig. 2); Gastroscopic diagnosis: Malignant ulcer of the gastric sinus with incomplete obstruction; Pathological diagnosis: poorly differentiated adenocarcinoma. Immunohistochemistry: Her-2(-); the tumour was classified as cTNM:cT4N+M0.

After conducting MDT discussions in Renji hospital, radical surgery for gastric cancer was recommended after termination of pregnancy. She was then induced in our Obstetrics and Gynaecology Department (22 + 1 weeks gestation), placenta-fetal membranes were sent for pathology for the presence of tumour cells. Pathology suggested: "placenta-fetal membranes", placenta membranes tissue with degeneration, no tumour tissue seen. On August 30, 2018, radical surgery for gastric cancer was performed (major distal gastrectomy with remnant gastrojejunostomy RY anastomosis, anterior colon, gastric D2 lymph node dissection). Intraoperatively, The gross appearance of the resected specimen was a tumour located in the anterior wall of the gastric body and the gastric sinus, with a size of about 4*5 cm in diameter, stiff, infiltrative ulcerative type, with a central deep concave ulcer, tumour breaking through the plasma membrane layer, invading part of the transverse colonic mesentery and the pancreatic capsule, and perigastric No 6, 7, 8, 9 and 12a lymph nodes were accessible and enlarged. No obvious metastatic lesions were found in the abdominal and pelvic cavities.
Postoperative pathological examination showed "poorly differentiated adenocarcinoma (diffuse infiltrative type, 6*5*1.2cm) on the side of the lesser curvature of the gastric sinus, invading the plasma membrane, pancreatic adhesions, cancerous thrombus in the ducts, invasion of nerves, lymph nodes of the lesser curvature (5/7), lymph nodes of the greater curvature (1/5), lymph nodes of "No 7" (1/4), lymph nodes of "No 8" (1/5), and in the "transverse colonic mesentery". The "upper and lower margins", the "hepatic ligament", the "No 4, 6 and 12a lymph nodes" were negative for fibrofatty tissue. Immunohistochemistry: CEA (+), P16 (++), Ki67 (80%), P53 (-), ER (-), PR (-), HER2 (-), PD-L1 (-, interstitial 5%), MLH1 (-), PMS2 (-), MSH2 (+), MSH6 (+) (Fig. 3a-f). According to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (Springer International Publishing, 8th Edition 2018), the tumour was classified as: pT4bN3M0, stage III C.

Unfortunately, one year postoperative follow-up revealed tumour recurrence. On August 4, 2019, CT enhancement of abdomen showed soft tissue mass measuring approximately 7.5cm*5.2cm, considered tumour recurrence/metastasis with possible involvement of duodenal stump, pancreatic head capsule, adjacent transverse colon mesentery; enlarged lymph nodes in the hilar region and retroperitoneum (Fig. 4a). On August 30, 2019, PET-CT similarly confirmed this result (Fig. 5). Due to the refusal of using any chemotherapy, the patient received pabrolizumab injection 100mg intravenous drip for the first time on September 3, 2019. After the treatment, abdominal CTA suggested a mass measuring approximately 6.4cm*6cm was seen on the right side of the mid-upper abdomen, which was significantly enhanced in a circular pattern with non-enhancing ground-density necrotic foci and gas shadows within, with scattered calcifications visible in the posterior superior wall and disappearance of the fatty gap with the surrounding intestinal canal (Fig. 4b).

On the day of pabrolizumab administration, she suffered a high fever of 39–40°C with chills, cough, dyspnea, profuse sweating, malaise, hypotension (systolic blood pressure 70 – 60 mmHg), SpO2 80–90%, WBC 19.87*10^9/L, N% 80.3%, Hepatorenal function is normal. Considering an infusion reaction or drug allergy to immunotherapy, aggressive symptomatic supportive therapy, physical hypothermia, oxygen inhalation, volume expansion and rehydration were given. 3 days later the patient’s symptoms were significantly relieved and the WBC (white blood cells) are also gradually decreasing in the routine blood tests.

Then, on August 29, 2019, the patient received pabrolizumab injection 100mg intravenous drip for the second time. On October 8, 2019, MRI enhancement of the abdomen suggested the soft tissue mass in the right upper abdomen measuring about 6.5cm*4.0cm (Fig. 6a). On October 19, 2019, the patient received pabrolizumab injection 100mg intravenous drip for the third time, the CTA for abdomen suggested patchy shadow of duodenum and parapancreatic head in the right upper abdomen, about 5.1cm*4.0cm in diameter, the duodenum and parapancreatic head lesion is smaller than 19-10-8, multiple lymph nodes in mesentery, hilar region and retroperitoneum (Fig. 6b). During November 11, 2019–February 24, 2020, the patient received pabrolizumab injection 100mg intravenous drip regularly, and the lesion had shrunk to 1.7cm in diameter (Fig. 6c).
The patient developed complications such as rash and vitiligo during this period, in addition, the patient had a myocarditis which resolved after treatment in the ICU. At subsequent follow-up, whole abdomen CTA (August 23, 2021) suggested that duodenal and parapancreatic head lesion reduced to 0.6 cm, full bilateral ovarian pattern, multiple lymph nodes in mesentery, hilar region and retroperitoneum (Fig. 6d).

Discussion

The group of pregnancy-related gastric cancer patients has received considerable attention in recent years. In general, gastric cancer has the fifth highest incidence of malignancies worldwide and is one of the four leading causes of cancer-related deaths\(^5\). Actually, gastric cancer is most commonplace in the middle-aged and elderly population (average age of prevalence is 60 years-old) and is less common in people under 40 years of age. Less than 15% of all gastric adenocarcinomas occur in adults younger than 41 years of age, and some scholars believed that the rare gastric cancer during pregnancy has the same features as in other patients under 40 years\(^6,7\).

Due to a great quantity of factors, the difficulty of diagnosing gastric cancer during pregnancy has increased significantly, making patients with gastric cancer during pregnancy often already at a progressive or even advanced stage when diagnosed, with an extremely poor prognosis for survival\(^8-10\). This has alerted the need to attach significance to gastrointestinal symptoms during pregnancy, conduct timely and comprehensive physical examinations, check tumour markers and perform fiberoptic gastroscopy to exclude gastric lesions\(^11-13\). For pregnant patients with gastric cancer, the timing of systemic chemotherapy intervention, when to perform surgical intervention to reduce the impact on the fetus during delivery, and the timing of treatment for the fetus during different trimesters are key areas for further research\(^14-16\). According to the relevant literature, most of the patients reported in China with gastric cancer in pregnancy are treated with SOX regimen chemotherapy after surgery. First-line chemotherapy regimens for patients with advanced disease are dominated by a combination of platinum and fluorouracil-based regimens, and second-line chemotherapy regimens containing irinotecan or raltitrexed\(^17\). Additionally, the results of several studies exerted that HER-2 positive patients with advanced gastric cancer will benefit from trastuzumab treatment. There are no significant difference in HER-2 expression and amplification between gastric cancer patients in pregnancy and non-pregnant ones. Therefore, HER-2 testing should be routinely recommended for patients with gastric cancer in pregnancy\(^18\).

However, to date, there are few reports of satisfactory outcomes with PD-1 inhibitors alone after surgery in gastric cancer patients during pregnancy, and there are no precise clinical guidelines recommending the use of PD-1 inhibitors alone. Furthermore, relevant studies have shown that the use of immune checkpoint inhibitors leads to an increased incidence of spontaneous abortion, stillbirth and preterm birth from the onset of fetal organ development to delivery\(^19,20\), and to date there have been only very few reports suggesting the use of immune checkpoint inhibitors in patients with melanoma in combination with pregnancy\(^21\). We provide the first case report of a satisfactory outcome with immunotherapy alone
in a patient with gastric cancer during pregnancy. This patient opted for termination of pregnancy and radical surgery, given a variety of subjective or objective factors, this case was refused conventional chemotherapy and received only immunotherapy alone. As a matter of fact, the discovery of tumour recurrence after surgical treatment in this case poses a greater challenge to the clinical surgeon. How should the treatment after recurrence be chosen? How about the choice of chemotherapy regimen? Is there an opportunity to consider re-surgical intervention? Does the patient still have a need for fertility and is in vitro fertilisation-embryo transfer considered again? It is pleasing to note that immunotherapy alone has shown promising results in controlling recurrent lesions during subsequent follow-up. The favourable outcome of patients with gastric cancer in pregnancy treated with PD-1 inhibitors alone may be related to the alteration of the immune microenvironment by pregnancy-related hormones. Moreover, some related reports have yet to mention a novel mechanism in trophoblasts to create a tolerant foetal-maternal interface by upregulating PD-L1. Tumours may also use PD-L1 expression to evade the host's immune response, thereby promoting their survival. Therefore, the application of PD-1 inhibitors may partially serve to disarm immune escape and strengthen anti-tumour immunity in gravida. But the exact mechanism needs to be further investigated[22]. In conclusion, the diagnosis and treatment of gastric cancer in pregnancy need to be balanced with multiple factors. This case report can provide some treatment options for related cases.

Conclusions

The treatment of pregnancy related gastric cancer is quite tricky in clinical practice.

In this case report, we focus a 32-year-old pregnant patient diagnosed with gastric cancer. Radical surgery was conducted after termination of pregnancy. One year postoperative follow-up exerted tumour recurrence, fortunately, this patient has achieved quite favourable outcome after receiving anti-PD-1 alone. For similar cases, questions such as when to intervene with systemic chemotherapy in pregnant patients with gastric cancer, when to perform surgical intervention with minimal impact on fetal delivery, how to weigh the timing of fetal treatments in different trimesters, and whether single-agent immunotherapy results in favorable outcomes are deserve to be studied in depth. This case report provides some treatment options for related cases.

Abbreviations

ICU
Intensive Care Unit
SOX regimen
oxaliplatin combination with S-1

Declarations

Ethics approval and consent to participate
The studies involving human participants were reviewed and approved by Informed consent was obtained from the patient. Research involving human subjects, human material, or human data, have been performed in accordance with the Declaration of Helsinki. The patients/participants provided their written informed consent to participate in this study.

**Consent for publication**

Written informed consent was obtained from the participants, and we confirm that the patients gave consent for their personal or clinical details along with any identifying images to be published in this study. Documentation of the written consent will be provided to the journal upon request.

**Data Availability**

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author/s.

**Conflict of interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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**Authors’ contributions**

XL and XQ collected the data, and wrote the manuscript. CC and LH performed the operation and designed the study. All authors read and approved the final version of the manuscript.

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**References**


Figures
Figure 1

Magnetic resonance imaging (MRI) detected a tumour in the gastric sinus. (As indicated by the red arrow, intersecting surface (a b); coronal position (c ).

Figure 2

Electron fibreoptic gastroscopy: Large ulcerated lesion of the gastric sinus, involving the four walls and the gastric angle, and the lesser curvature of the gastric body.
Figure 3

Immunohistochemistry: The pathological picture of tumor confirmed under 40× microscope (a), PD-L1 (-, interstitial 5%) (b), MLH1 (-) (c), PMS2 (-) (d), MSH2 (+) (e), MSH6 (+) (f).
Figure 4

CT enhancement of abdomen showed tumour recurrence (a), after received pabrolizumab therapy (b).
Figure 5

PET-CT detected a tumour recurrence in the right upper abdomen.
Figure 6

The patient received pabrolizumab injection 100mg intravenous drip regularly. Magnetic resonance imaging (MRI) and enhanced computed tomography (CT) exerted the lesion shrinking gradually (a-d).