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CASE REPORT

Disseminated carcinomatosis of the bone marrow from gastric cancer during pregnancy

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Abstract
Gastric cancer during pregnancy is extremely rare and difficult to diagnose at early stages because of its nature. Furthermore, it is often difficult to determine the appropriate treatment strategy considering both the patient's condition and the effect of the treatment on the fetus. We present a case of a 34-year-old woman with gastric cancer who was 22 weeks pregnant and had multiple liver and bone metastases at the time of diagnosis. The disease progressed to disseminated carcinomatosis of the bone marrow, in which cancer invades and spreads diffusely to the bone marrow and then presents disseminated intravascular coagulation. Fortunately, the selected systematic chemotherapy dramatically reduced the severity of the patient's cancer and she could deliver her baby successfully. There are few reports of disseminated carcinomatosis of the bone marrow from gastric cancer during pregnancy. Even in such an oncological emergency, prompt chemotherapy saved the mother's life and enabled safe delivery of the fetus.

Keywords Gastric cancer · Pregnancy · Disseminated carcinomatosis of the bone marrow · Chemotherapy

Introduction

Gastric cancer during pregnancy is extremely rare [1, 2] and tends to be diagnosed at an advanced stage, because it is difficult to distinguish typical symptoms of gastric cancer from pregnancy-induced symptoms, such as nausea, vomiting, and abdominal discomfort, which leads to poor prognosis. The treatment of gastric cancer during pregnancy is complicated, because the safety of both mother and fetus should be considered. Here, we report the case of a 22 weeks pregnant woman who was diagnosed with advanced gastric cancer and presented with multiple liver and bone metastases. Although her condition progressed to disseminated carcinomatosis of the bone marrow (DCBM), the selected systematic chemotherapy dramatically improved the severity of the patient's cancer and she successfully delivered a healthy baby without malformations.

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Case report

A 34-year-old woman who was 22 weeks pregnant noted continued lumbar and chest pain, which was initially diagnosed to be associated with her pregnancy. After a few weeks, she was admitted to an emergency room with the same chief complaint because her pain became worse. She was diagnosed with advanced gastric cancer and presented with multiple liver and bone metastases at the hospital. She was referred to our hospital for further examination and treatment.

When she was admitted to our hospital, she was 23 weeks pregnant and her fetal state was normal. However, her Eastern Cooperative Oncology Group performance status was 4, i.e., completely disabled, cannot carry on any selfcare, and totally confined to bed or chair because of the pain. The laboratory findings indicated disseminated intravascular coagulation (DIC) syndrome (scored as 5 points or more by the International Society on Thrombosis and Haemostasis's diagnostic criteria for DIC) and elevated levels of tumor markers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) (Table 1). An upper gastrointestinal endoscopy revealed poor extension of the gastric wall and giant gastric folds, which indicated that she had

Table 1 Blood biochemical findings

CBC	
WBC	15,700/μL
RBC	233×10^4/μL
Hb	7.1 g/dL
Hct	20.8%
Plt	8.1×10^4/μL
Erythroblast	+
Coagulation test	
PT	126%
APTT	31.5 s
Fib	417 mg/dL
FDP	115.4 μg/dL
D-Dimer	47.5 μg/dL
Tumor marker	
CEA	41.3 ng/mL
CA19-9	378.6 U/mL
CA125	55.7 U/mL
STN	4703.5 U/mL
Biochemistry	
TP	5.5 g/dL
Alb	1.9 g/dL
Na	136 mEq/L
K	3.0 mEq/L
CI	95 mEq/L
Ca	8.2 mEq/L
BUN	14.0 mg/dL
Crea	0.35 mg/dL
T-bil	0.6 mg/dL
AST	64 IU/L
ALT	24 IU/L
LDH	4689 IU/L
ALP	1738 IU/L
γ-GTP	55 IU/L
Amy	234 IU/L
BUN	14.0 mg/dL
CRP	13.67 mg/dL
Crea	0.35 mg/dL

Bormann type IV gastric cancer (Fig. 1a). The histological examination of biopsy specimens showed a poorly differentiated adenocarcinoma with signet ring cells and the human epidermal growth factor receptor 2 (HER-2) was positive (IHC3+, Fig. 1b). Computed tomography (CT) showed a thickened gastric wall, multiple abdominal lymphadenopathy, multiple low density lesions with irregular shape in the liver (Fig. 2a), and multiple widespread low-density mass with compression fractures in the vertebral bones (Fig. 2b). The compression fractures of the vertebral bones were supposed to be caused by bone metastasis, because the patient was a healthy young woman and had no episode of trauma or other past medical histories. Although we could not perform bone biopsy because of the patient's poor condition, we clinically diagnosed that her condition progressed to DCBM, which is characterized by the triad of anemia, back dorsal pain, and bleeding tendency, and accompanied by elevation of serum alkaline phosphatase and alkaline phosphatase. The patient needed to receive life-saving systemic chemotherapy as soon as possible because of her poor prognostic situation. We obtained informed consent and the patient decided to receive systemic chemotherapy while continuing her pregnancy despite the increased teratogenic risk to her fetus.

The patient received the combination chemotherapy of S-1 and oxaliplatin with trastuzumab as the first-line regimen which was administered on day 1 (i.e., S-1: 80 mg/day from day 1 to day 14 with 130 mg/m^2 oxaliplatin and 8 mg/kg trastuzumab). After one cycle, the patient's condition improved dramatically. Her general status, laboratory data, and serum levels of CEA and CA19-9 showed improvement. Her DIC was cured after 2 days of chemotherapy (DIC score, 1 point).

Her fetus developed normally during the treatment. Therefore, delivery was planned at 34 weeks of gestation after 4 cycles of chemotherapy. On day 73 of hospitalization, a healthy boy weighing 1938 g was delivered via cesarean section. The newborn developed normally, although he required temporary mechanical ventilation just after birth. He was discharged from hospital 10 days after birth without hematological or physical problems (Fig. 3).

The patient resumed the same chemotherapy 8 days after delivery. After two cycles, the accumulated ascites and pleural effusion had worsened. Additionally, multiple liver metastases had also worsened, as shown by CT. Her chemotherapy regimen was changed to the combination chemotherapy of paclitaxel and ramucirumab as the second-line regimen. However, the patient's physical condition worsened and she had respiratory insufficiency and acute liver failure after two cycles of chemotherapy. The patient died 209 days after the start of treatment and 126 days after her son's birth.

Discussion

Cancer during pregnancy is extremely rare and has an incidence of approximately 0.1% [1]. The incidence of gastric cancer is lower at about 0.026–0.1% of all pregnancies [1–3]. Furthermore, the presented case was extremely rare, i.e., the disease progressed to DCBM with DIC during pregnancy. Fortunately, the immediate chemotherapy enabled the fetus's safe delivery despite the oncological emergency in this case. This is the first report that patients with cancer during pregnancy can safely deliver a fetus in such a poor prognostic situation.

The prognosis of gastric cancer during pregnancy is extremely poor, with 1- and 2-year survival rates of 18.0%

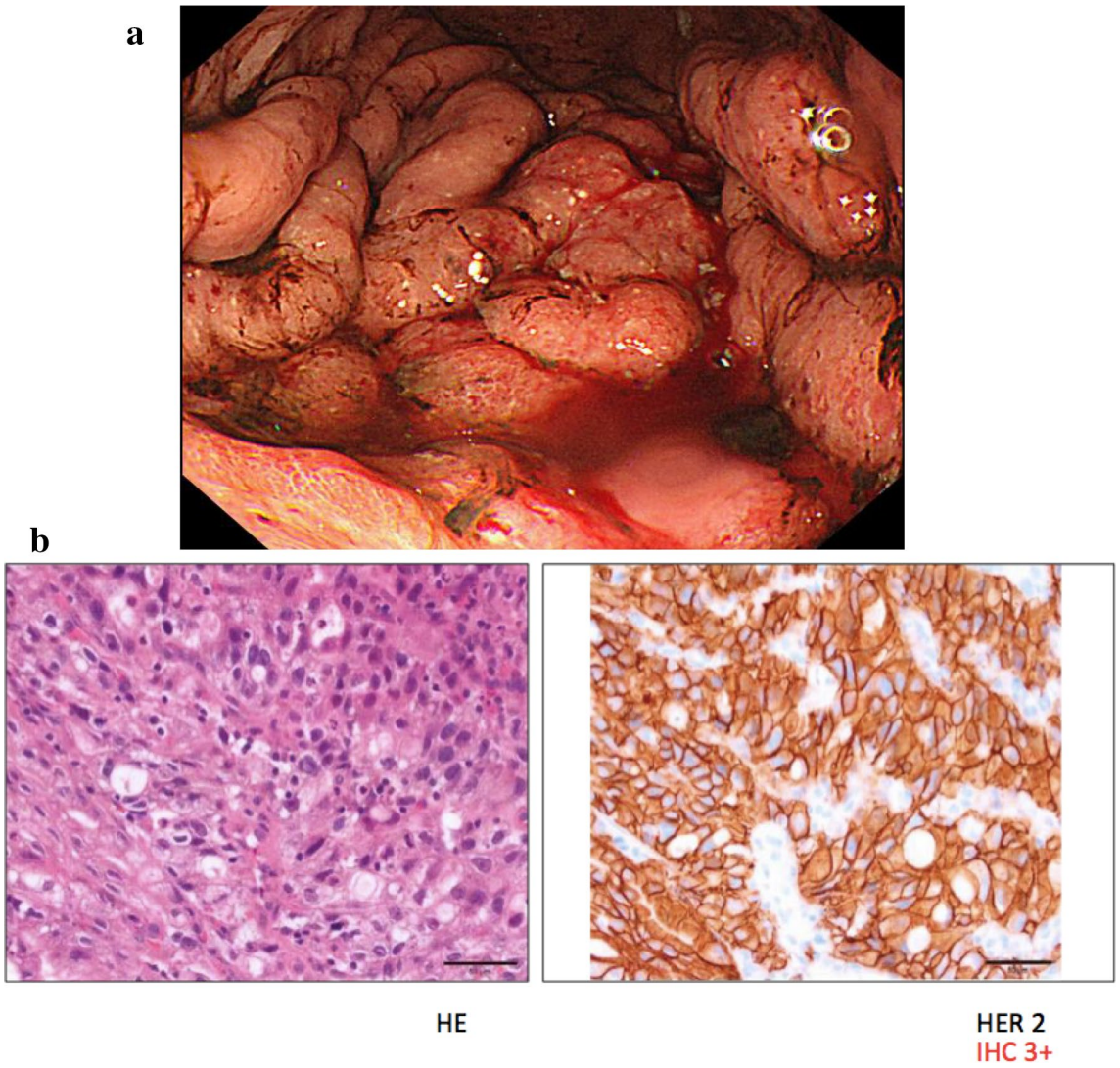

Fig. 1 **a** Upper gastrointestinal endoscopy findings. Poor extension of the gastric wall and giant gastric folds. **b** The histological examination of gastric biopsy specimens. Poorly differentiated adenocarcinoma with signet ring cell carcinoma and HER-2 status was positive (IHC 3+). *HER-2* human epidermal growth factor receptor 2

and 15.1%, respectively [1]. This is because the symptoms of gastric cancer with pregnancy are nonspecific, e.g., nausea or vomiting, and it is difficult to distinguish from symptoms peculiar to pregnancy, leading to delay in diagnosis [1–3]. Additionally, the treatment of those patients is also challenging. It is recommended to have an abortion before 22 weeks of gestation and to early parturition after 28 weeks of gestation in starting the treatment. However, the recommended treatment strategy from 22 to 28 weeks of gestation is controversial. The immediate treatment including systemic chemotherapy is beneficial for patients, whereas there is a possibility that adverse events to the fetus might occur [1, 2]. It is necessary to flexibly develop a treatment strategy that considers the condition of the patient and the development of the fetus.

In addition to the pregnancy, the disease progressed to DCBM in this case. DCBM is caused by solid tumor metastasis and approximately 90% of all DCBM are derived from gastric cancer [4]. Unlike general bone metastasis, the pattern of metastases in DCBM is diffuse infiltration instead of a nodular pattern and it causes hematological disorders, such as DIC, leukoerythroblastosis, and microangiopathic hemolytic anemia. We should have performed the bone marrow biopsy for histopathological diagnosis of DCBM. However, we could not perform the bone marrow biopsy due to the patient's poor general conditions. Furthermore, the patient's platelets decreased to 37,000 μL due to the rapid progress of DIC and the risk of bleeding associated with the puncture was extremely high. Notably, this case presented several clinical features of DCBM such as DIC,

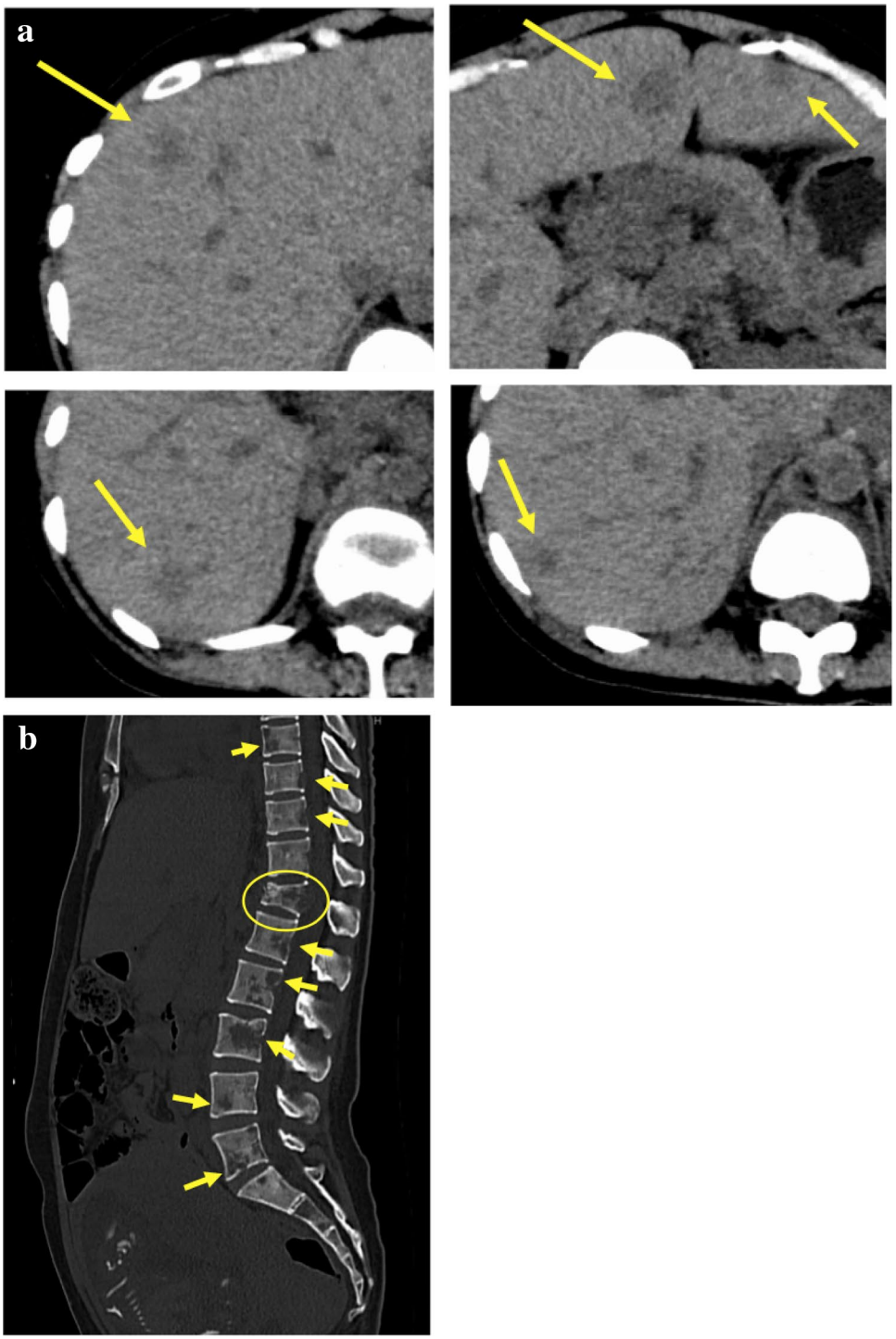

Fig. 2 Computed tomography findings. **a** Multiple low-density lesions with irregular shape in the liver (arrows). **b** Multiple widespread low-density mass in the vertebral bone (arrows) and compression fractures (circle)

leukoerythroblastosis, anemia, elevation of serum ALP and LDH, widespread bone metastases as described above. Therefore, it was clinically diagnosed as DCBM from GC during pregnancy.

The prognosis of DCBM is reported to be extremely poor, with a median survival time of 3.1 months [5]. The median overall survival of advanced gastric cancer with DIC was reported to be 5.74 months [6], despite the recent development of systemic chemotherapy. Furthermore, some patients with DCBM were reported to die within a few weeks due to bleeding or organ insufficiency caused by DIC [6]. Thus, the patient was not only a case of gastric cancer during pregnancy, but also experienced an oncological emergency. Although Kurabayashi et al. were the first to report a case of a patient with gastric cancer during pregnancy with DIC, which is like our case, unfortunately, their patient died on

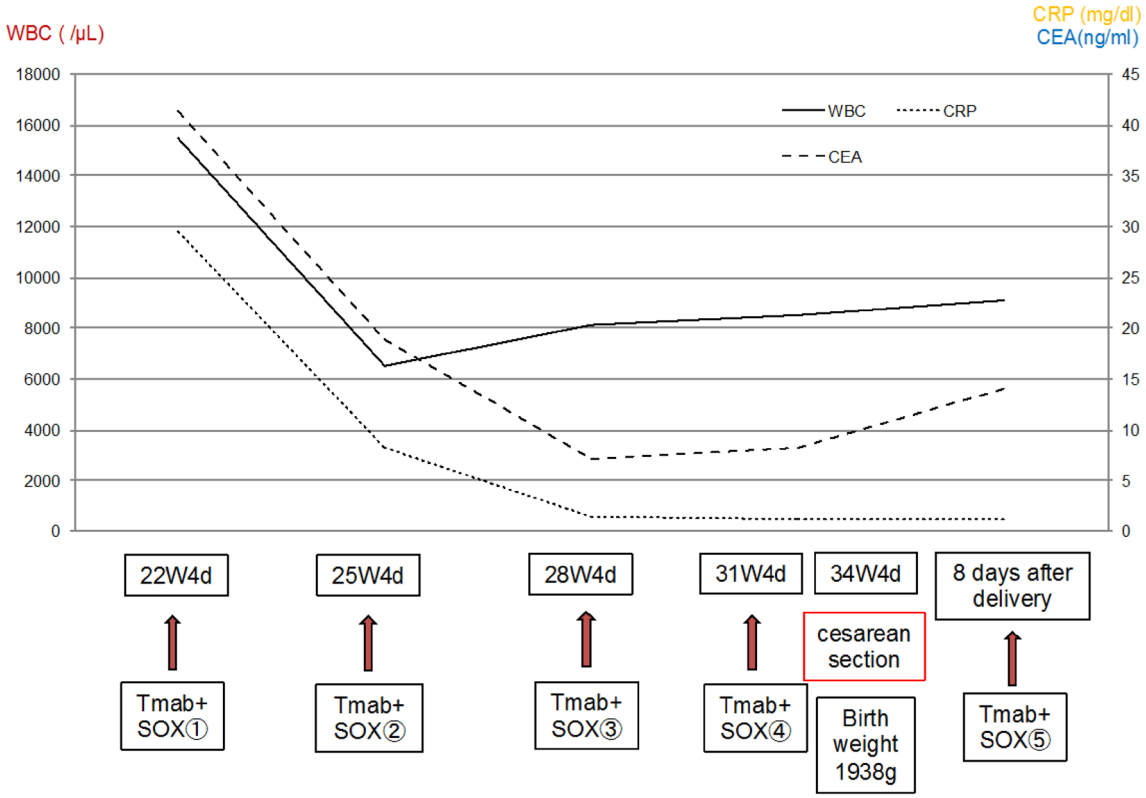

Fig. 3 The change of hematological parameter and tumor marker during the systemic chemotherapy. *Tmab* trastuzumab, *SOX* S-1 and oxaliplatin

the 13th day postpartum [7]. Several reports have indicated that aggressive chemotherapy leads to survival benefits for patients with DCBM [8]; therefore, we immediately started systemic chemotherapy to save the patient's life despite her pregnancy.

In starting a systematic chemotherapy treatment, the effect of anticancer drugs on the fetus should be considered. The combination regimen of trastuzumab with fluoropyrimidine and platinum is recommended as a first-line therapy for metastatic HER2-positive gastric cancer [9]. However, there is no recommended regimen for pregnancy. The administration of 5-fluorouracil or oxaliplatin in the second and third trimesters demonstrated almost no risk of adverse events [10]. On the other hand, several reports found that cisplatin caused adverse events to the fetus, such as intrauterine growth retardation, hearing loss, and ventriculomegaly [10, 11]. Moreover, a large amount of intravenous hydration is necessary to prevent renal toxicity when cisplatin is used, which would worsen hydronephrosis, ascites, and pericardial effusion. Therefore, it might be advisable to avoid cisplatin for pregnant women with cancer. Besides, systematic reviews and meta-analyses have also found that oligohydramnios or hydramnios were adverse events following exposure to trastuzumab during the second and third trimesters. Therefore, avoiding the use of trastuzumab during pregnancy is recommended by some studies [11]. In one review, however, the use of trastuzumab improved the pregnancy outcome for both mother and her fetus compared with standard chemotherapy [12]. Therefore, we selected a combination chemotherapy of S-1 and oxaliplatin with trastuzumab as the first-line regimen in this case, considering the maximal therapeutic effect for the patient and minimal adverse events to the fetus.

In conclusion, we herein report the first patient to be successfully treated by systemic chemotherapy leading to a temporary recovery from her life-threatening condition to deliver her child and survive for 7 months after the start of treatment. In this oncological emergency, prompt chemotherapy was able to save the mother's life and enable safe delivery of the fetus.

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Compliance with ethical standards

Conflict of interest Shotaro Kinoshita, Kohei Yamashita, Masaaki Iwatsuki, Hiroki Sato, Chihiro Matsumoto, Takashi Matsumoto, Yuta Shiraishi, Naoya Yoshida and Hideo Baba declare that they have no conflicts of interest.

Human rights All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed consent Informed consent was obtained from the patient for this study.

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