



# Advanced metastatic gastric adenocarcinoma identified within the placenta: a case report with literature review

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**Abstract:** We present an extremely rare case of a multiparous women age 32 in her 35th week of gestation who was admitted to our hospital for evaluation of back pain and was incidentally found to have metastatic gastric adenocarcinoma, diagnosed from a routine placental specimen. The coexistence of gastric carcinoma with pregnancy is a rare event, accounting for 0.026% to 0.1% of all pregnancies. To the best of our knowledge, the world literature contains only eight known cases of metastatic gastric cancer to the placenta—the present case is the ninth. An uncommon finding, in this case, was the extensive spread of cancer to bone marrow and leptomeninges.

**Keywords:** Gastric adenocarcinoma; pregnancy complications; placental disease; leptomeningeal involvement; bone metastasis

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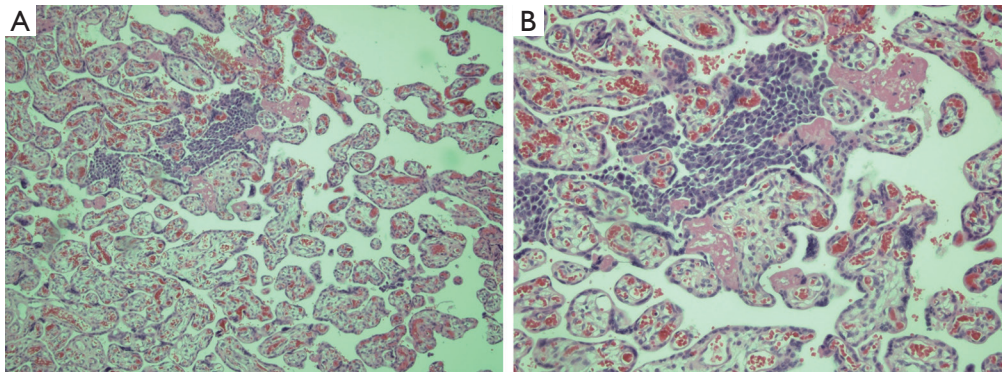
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## Introduction

A 32-year-old woman, gravida 5, para 4 presented in her 35th week of gestation for evaluation of back pain. Prior to this visit, her pregnancy was uneventful. The patient's medical history and family history was unremarkable. Labs were significant for alkaline phosphatase (ALP) 251 U/L, total bilirubin (T-bili) 1.2 mg/dL, lactate dehydrogenase (LDH) 728 U/L, uric acid 8.4 mg/dL, fibrinogen 157 mg/dL, international normalized ratio (INR) 1.5, prothrombin time (PT) 17.8 s, partial thromboplastin time (PTT) 35.8 s, platelet count (PLT) 33 K/ $\mu$ L, reticulocyte count 2.4% with peripheral smear significant for normochromic normocytic red blood cells without schistocytes, and no laboratory evidence of ADAMSTS-13 deficiency. Her labs were concerning for disseminated intravascular coagulation (DIC)/hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome, prompting an urgent cesarean section. The placenta was sent for pathological examination as part of the evaluation of this high-risk pregnancy. Cross section of the placental disk showed areas with intervillous and sub-chorionic fibrin

deposition. In addition, scattered clusters of tumor cells were present within the intervillous spaces. The tumor cells had large somewhat eccentrically placed nuclei, irregular nuclear contours, and prominent nucleoli. The tumor appeared confined to the intervillous spaces, and no villous stromal invasion by tumor was seen (*Figure 1A,B*). A panel of immunohistochemical stains was positive for Ber-Ep4, cytokeratin 7 and MUC5AC, confirming a diagnosis of metastatic carcinoma. Computed tomography (CT) of the patient's chest, abdomen, and pelvis with intravenous (IV) contrast reported a prominent nodular thickening of the anterior gastric body and antrum suggesting a mass (*Figure 2*). Magnetic resonance imaging (MRI) of the patient's brain showed no evidence of metastasis. An MRI of her L-spine was significant for diffuse marrow signal changes compatible with hematopoietic bone marrow. The patient subsequently underwent esophagogastroduodenoscopy (EGD) revealing a large, fungating and ulcerated, non-circumferential mass in the gastric antrum. A biopsy of the EGD mass showed similar histological features and demonstrated an infiltrate of malignant signet ring type cells in the lamina propria.



**Figure 1** Placental histopathology. 100× (A) and 200× (B) section of the placental disk show areas in intervillous and subchorionic fibrin deposition. In addition, scattered clusters of tumor cells are present within the intervillous spaces. The tumor cells have large somewhat eccentrically placed nuclei, irregular nuclear contours, and prominent nucleoli. The tumor appears confined to the intervillous spaces, and no villous stromal invasion by tumor was seen.



**Figure 2** Computed tomography with contrast of gastric body and antrum shows prominent nodular thickening of the anterior gastric body and antrum.

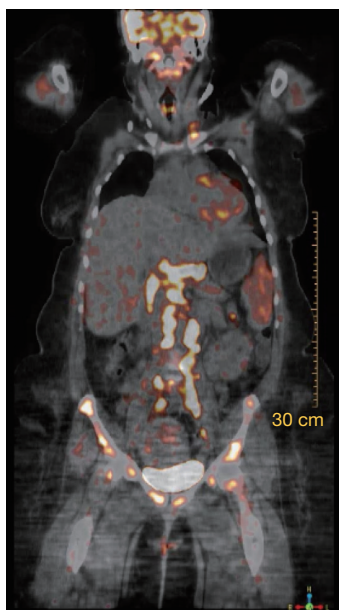
Tumor DNA sequencing showed *KRAS*, *NRAS*, *BRAF*, *EGFR*, *HER2neu* negative, with low mutation burden and microsatellite stable. A positron emission tomography-CT (PET-CT) scan found a hypermetabolic gastric antral lesion with extensive hypermetabolic lymphadenopathy in the periportal, retroperitoneal para-aortic, inferior mediastinal and left supraclavicular regions (Figure 3) along with diffusely increased bone marrow activity throughout the pelvis, vertebral bodies, and sternum (Figure 4).

The patient was started on palliative FOLFOX as an inpatient. At times, treatment was delayed due to side effects and decreased quality of life affecting the patient's

ability to take care of her children. Four months later, a repeat PET scan showed residual wall thickening in the antral region of the stomach with almost complete interval resolution of the previously reported extensive metastatic lymphadenopathy in the abdomen, inferior mediastinum, and left supraclavicular regions. However, there was new, extensive ostial metastatic involvement in the thoracic and lumbar vertebrae, sternum, bilateral ribs, bilateral scapula, pelvis, and bilateral femur. There was also a prominent focus in the left posterior aspect of T11 vertebral body projecting into the adjacent spinal cord (Figure 5). The patient had no signs or symptoms of compression or spinal cord involvement but had considerable pain near the T11 vertebral region.

Two months later, the patient was readmitted with severe back pain, weakness of bilateral legs, and numbness of the left cheek extending to the gums and left lower eyelid (V2 distribution).

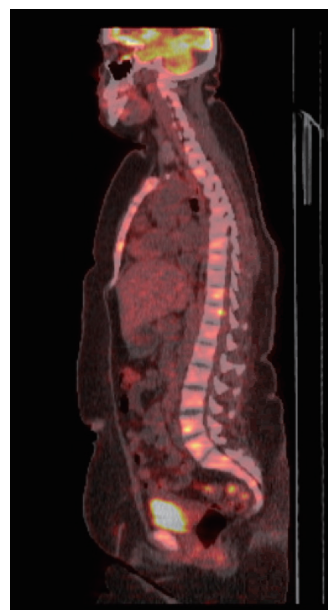
An MRI of her spine revealed infiltrates throughout the cervical, thoracic, and lumbar spine. An MRI of her brain showed no masses; however, a new pachymeningeal (dura-arachnoid) enhancement was seen. The patient underwent a lumbar puncture (LP) study, which was interpreted as having few atypical cells, highly suspicious for metastatic adenocarcinoma. The patient was diagnosed with malignant carcinomatous meningitis and started on with palliative radiation to the spine and intrathecal methotrexate. Her disease progressed rapidly, and she was placed on hospice with pain management. Approximately 7 months following diagnosis, she expired. A follow-up exam of the newborn at



**Figure 3** PET-CT with hypermetabolic gastric lesion with extensive lymphadenopathy. Hypermetabolic mass like thickening in the gastric antrum; extensive hypermetabolic periportal/porta hepatis conglomerated adenopathy with extensive hypermetabolic retroperitoneal adenopathy throughout the abdomen. PET-CT, positron emission tomography-computed tomography.



**Figure 4** Increased bone marrow activity throughout the pelvis, vertebral bodies, and sternum.



**Figure 5** T11 ostial metastasis. T11 vertebrae projecting into adjacent spinal canal.

9 months found no evidence of metastasis.

## Discussion

Gastric cancer is one of the deadliest diseases and frequently offers a poor prognosis. With only 31.0% of cases surviving 5 years. Based on 2011–2015 cases, the number of new cases of stomach cancers per year was 7.2 per 100,000 men and women. Based on 2013–2015 data, approximately 0.8% of men and women will be diagnosed with stomach cancer. In 2018, there were 26,240 estimated new cases; 1.5% of all new cancer cases (1).

The coexistence of gastric carcinoma with pregnancy is rare; depending on the region of the world it accounts for anywhere between 0.026% to 0.1% of all pregnancies (2). Placental metastasis from maternal cancer is even rarer. Our search showed since Friedreich reported the first case of carcinoma metastasized to the fetus in 1866 (3) there have been only 36 reported cases of gastric cancer metastasis. Furthermore, the worldwide literature notes only 8 reported cases (see *Table 1*) of metastatic gastric cancer to a placenta. To our knowledge, in addition to placental metastasis, not a single reported case included metastasis to bone and leptomeninges, as in our case. Making this the first case

**Table 1** Literature review of gastric cancer metastasis to placenta in pregnancy

Case	Author	Age (years)	Gestational age (weeks)	Histological type	Metastasis elsewhere	Child outcome	Fetal metastasis	Maternal outcome
1	Chen <i>et al.</i> (4)	35	34	Intermediate differentiated gastric adenocarcinoma	Absent	Survived, no metastasis	Absent	Survived
2	Khatib <i>et al.</i> (5)	26	26	Poorly differentiated gastric adenocarcinoma	Peritoneal, hepatic and diaphragm	Survived, no metastasis	Absent	Death
3	Baker <i>et al.</i> (6)	22	28	Undifferentiated carcinoma with scattered signet cells	Right ovary	Survived, no metastasis	Absent	Death
4	Yoshida <i>et al.</i> (7)	32	22	Poorly differentiated adenocarcinoma	Hepatic	Survived, no metastasis	Absent	Survived
5	Miller <i>et al.</i> (8)	35	22	Poorly differentiated adenocarcinoma	Spinal metastases	Survived, no metastasis	Absent	Death
6	Senge (9)	Unknown	Unknown	Unknown	Unknown	Unknown	Absent	Unknown
7	Lee <i>et al.</i> (10)	27	27	Poorly differentiated adenocarcinoma	Disseminated bone metastasis	Survived, no metastasis	Absent	Death
8	Lee <i>et al.</i> (11)	28	22	Poorly differentiated adenocarcinoma	Unknown	Survived, no metastasis	Absent	Death

of placental metastatic disease with a complex metastatic presentation involving extensive bone marrow involvement and leptomeningeal disease.

Gastric cancer associated with pregnancy is generally discovered at an advanced stage and consequently has a dismal prognosis. The poor prognosis of gastric cancer during pregnancy is derived from its rarity and delayed diagnoses secondary to symptoms interpreted as a part of normal physiological gestational symptoms, such as nausea, vomiting or abdominal pain or cramping (12). Of 92 cases of gastric cancer reviewed by Jaspers *et al.* (13), only two cases were found to be diagnosed early stage. Rapid progression and later diagnosis lead to a poor prognosis for these women, with 88.0% of patients expiring from the disease within 1 year.

Further, summarizing a total of 61 Japanese gastric cancer cases during pregnancy, Ueo *et al.* (14) reported about 97% of patients were at an advanced stage with a 21.1% 3-year survival rate. Based on their experience and review of the literature, the authors concluded that the poor prognosis for gastric cancer during pregnancy is a result of the favorable environment for the disease caused by estrogen surges, the immunosuppressive effect of pregnancy, limited therapeutic approaches, and the likelihood of delayed diagnosis.

In the present case, the patient was not known to have any prior malignancies and fetal development was

progressing normally. The patient developed HELLP/DIC; therefore, we prioritized the mother's survival and elected for a cesarean section. Our patient's gastric mass biopsy indicated advanced-stage adenocarcinoma with signet ring cells that were not amiable to surgical intervention. However, for cases when gastric cancer is diagnosed early, it would usually be preferable to perform endoscopic surgery and continue the pregnancy for as long as possible.

The most common metastatic sites for gastric carcinoma are peritoneal surfaces, the liver, spleen, ovaries, lung, and brain. Gastric cancer infrequently metastasizes to the bone. This report describes an extremely rare case of progressive osseous metastasis. In comparison to other solid tumors, osseous metastasis in gastric cancer patients has been shown to exhibit poor prognosis, with a mean survival time of <5 months (15,16). Patients often suffer from extensive bone pain affecting the quality of life. Due to the extensive capillary network in the gastric mucosa and lack of lymphatic vessels in the bone marrow, the metastatic pathway of gastric cancer cells is generally hematogenous (17). High proliferation in bone marrow, causes disseminated carcinomatosis a majority of the time, as in our case. Cases of bone marrow metastatic spread occur most commonly with signet ring cell type or undifferentiated type. In a study by Ahn *et al.* (18), it was found that 19 of 2,150 patients with gastric carcinoma

expressed metastasis to the bone (0.9%). All these cases suggest a relationship between poor differentiation and signet-ring type carcinoma and unusual locations for metastasis (18).

Leptomeningeal involvement is also very unusual and is considered a devastating outcome of gastric cancer. Our patient had a radiological abnormality of her pachymeningeal (dura-arachnoid) and cytological evidence of malignancy in the cerebrospinal fluid. Leptomeningeal carcinomatosis (LC) presents in approximately 2% to 4% of all patients with cancer, but its incidence is much lower in gastric carcinoma (19). Based on Vergoulidou's literature review, LC is associated with incredibly poor prognosis and because of its rarity, there are limited treatment modalities. Leptomeningeal involvement often results in rapid deterioration refractory to conventional and intrathecal chemotherapy.

Fortunately, the patient's newborn did not have any evidence of metastasis likely due to biological protective mechanisms. Maternal and fetal circulation are separated by the syncytiotrophoblasts (outer layer), the cytotrophoblasts (inner layer) that line the villous projections and the capillary wall. Maternal blood circulation in the placenta drains into the intervillous space, where the anchoring villous projections are located. Wang *et al.* (20), examined morphological changes of the placenta from a case of maternal acute lymphatic leukemia concluding that syncytium could play a role as a physical barrier in the prevention of vertical transplacental metastasis by phagocytosis and destruction of tumor cells. Wang *et al.*, made this conclusion based on discovering phagocytosis of nucleus-containing cells by the syncytiotrophoblast, cells with an abundant number of microtubular bundles within the villous stroma and dilatation of syncytial rough endoplasmic reticulum, numerous syncytial knots, and numerous autophagosomes.

In addition to trophoblasts, another defense mechanism may exist in the placenta to inhibit fetal metastasis. Literature has proposed that a primitive connective tissue, Wharton's Jelly, laying between the amniotic epithelium and the umbilical vessels has been found to have human umbilical cord mesenchymal stem cells (hUCMSCs). (21) These cells are characterized by their self-renewal and multipotency. In *in vitro* and *in vivo* hUCMSC have proved to suppress tumorigenesis. The underlying mechanism is likely related to cell cycle arrest, stimulation of tumor cell apoptosis, and suppressed activities of protein kinases (22).

In conclusion, gastric carcinogenesis is a multistep and

multifactorial process. While gastric cancer remains a deadly disease, the discoveries of new molecular markers, genetic and epigenetic alterations, and novel pharmacogenetic traits have facilitated improvement in patient care, fostered hope, and paved new directions. Thus, the potential for gastric carcinoma in pregnancy should not be ignored, particularly in females presenting with atypical digestive symptoms in later trimesters. Patients need early intervention to improve prognosis. We recommend a low threshold for screening.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Informed consent was obtained from the patients next of kin for publication of this case report and any accompanying images.

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