

Signet Ring Cell Carcinoma with Lymphangitic Carcinomatosis in Pregnancy: A Case Report of an Unexpected Maternal Death and Review of the Literature

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: Female, 26-year-old
Final Diagnosis: Adenocarcinoma with signet-ring cell features
Symptoms: 32 week gestation with new onset chest pain and shortness of breath
Medication: —
Clinical Procedure: —
Specialty: Obstetrics and Gynecology





Objective: Rare co-existence of disease or pathology
Background: Cancer in pregnancy is extremely rare, and gastric cancers are rarer still. Diagnosis is difficult in pregnancy due to overlapping symptoms with pregnancy such as nausea, pain, anemia, and fatigue.

Case Report: A 26-year-old G1 woman at 32 weeks gestation with a past medical history of systemic lupus erythematosus presented with new-onset chest pain and shortness of breath. Computed tomography of the chest, electrocardiogram, and echocardiogram were normal. Laboratory evaluation revealed thrombocytopenia, proteinuria of 480 milligrams, and normal complement. She delivered on hospital day 3 due to worsening chest pain. During cesarean delivery, the patient became hypotensive and hypoxic and required intensive care unit admission after a cesarean hysterectomy. On postoperative day 2 she had a pulmonary embolus and was started on therapeutic anticoagulation. She clinically improved until postoperative day 4, when she was found unresponsive with pulseless electrical activity. After 38 minutes of Advanced Cardiac Life Support, death was pronounced. An autopsy was performed and the cause of death found to be complications of multi-organ system involvement of adenocarcinoma with signet ring cell features. Lymphangitic carcinomatosis was noted throughout the lungs.

Conclusions: This patient had adenocarcinoma with signet ring cell features and associated lymphangitic carcinomatosis, which led to her postpartum death. Lymphangitic carcinomatosis is associated with an exceedingly poor prognosis, especially in pregnancy.

MeSH Keywords: Carcinoma, Signet Ring Cell • Maternal Mortality • Neoplasm Metastasis • Pregnancy Complications, Neoplastic

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Background

Cancer in pregnancy is extremely rare, with 0.001–0.09% of pregnancies being affected [1,2]. Rarer still is gastric carcinoma, which has an incidence of 0.2/100 000 pregnancies [2]. Diagnosis of cancer in pregnancy is difficult and can be delayed due to comparable symptoms such as nausea, abdominal pain, anemia, and fatigue [3]. We present a case of metastatic signet ring cell carcinoma with lymphangitic carcinomatosis that was diagnosed at autopsy after maternal death on postpartum/postoperative day 4. Overall, the maternal mortality rate in the United States is estimated to be 18 per 100 000 births [4]. In approximately 6.5% of all maternal deaths, the cause is unknown [4]. Without autopsy, our case likely would have ended up either wrongly categorized or without a known cause.

Case Report

A 26-year-old female gravida 1 was referred to our institution at 14 weeks' gestation by last menstrual period, consistent with a 9-week ultrasound for supervision of high-risk pregnancy secondary to maternal history of systemic lupus erythematosus (SLE). Outside records revealed positive ANA with elevated SSA >8 and SSB of 1.6 (normal SSA and SSB <1). Physical examination at time of initial presentation to our institution was consistent with a normally developed young woman, normotensive, with a BMI of 26. Physical examination at that time was unremarkable. Baseline pregnancy-induced hypertension lab work at 15 weeks' gestation was within normal limits and 24-hour urine collection was 150 mg of protein. An echocardiogram demonstrated normal cardiac structure and function, with an ejection fraction of 60%. Targeted ultrasound evaluation at 22 weeks' gestation revealed a normal fetal anatomic survey, growth, and amniotic fluid volume. A fetal echocardiogram was normal.

At 32 weeks' gestation the patient presented to a clinic with complaints of new-onset chest pain and shortness of breath with palpitations and new-onset proteinuria. She was admitted to the hospital for further evaluation, with a leading differential diagnosis of preeclampsia versus lupus flare. Lab work revealed thrombocytopenia (69 000), 24-hour urine protein of 480 milligrams, and normal C3/C4 complement levels. She was normotensive, but required supplemental oxygen to maintain oxygen saturations >95%. Computed tomography (CT) protocol to diagnose pulmonary embolus was performed, with no central segmental pulmonary embolus demonstrated. Bilateral ground-glass changes with peri-bronchovascular nodularity and mediastinal hilar lymphadenopathy were noted (Figure 1). Echocardiography was repeated and again demonstrated normal cardiac structure and function, with an ejection fraction of 60%. Azithromycin and ceftriaxone were initiated for possible community-acquired pneumonia.



Figure 1. Computed tomography of chest with mediastinal hilar lymphadenopathy. The largest lymph node measured 1.5 cm in the subcarinal space.

In the setting of normal complement and no other signs of lupus on exam, the leading diagnosis was atypical preeclampsia and the decision was made to proceed with delivery on hospital day 3 due to worsening symptoms and lab results. She underwent primary low transverse cesarean section and delivered a viable female infant with Apgar scores of 7 and 8 and weight of 2020 grams. Immediately following delivery, the patient clinically decompensated, becoming hypotensive and hypoxic, requiring resuscitative measures with vasopressors, transfusion of blood products, and intubation. The immediate postpartum course was also complicated by uterine atony, and she subsequently underwent supra-cervical hysterectomy after no improvement with conservative management, including bimanual uterine massage, utero-tonic medication (carboprost), and B-lynch suture placement. On postoperative day 1, her course was complicated by continued postpartum hemorrhage requiring bilateral uterine artery embolization. Resuscitative efforts beginning intra-operatively and extending through postoperative day 2 were guided by serial rotational thromboelastometry (ROTEM) and included a total of 5 units packed red blood cells, 7 units of fresh frozen plasma, 3 units of cryoprecipitate, and 3 units of platelets. A CT pulmonary embolus protocol was performed on postoperative day 2 due to complaint of sudden-onset shortness of breath with associated tachypnea and hypoxia. The CT demonstrated bilateral pulmonary emboli with right heart strain (significant right ventricular enlargement) (Figure 2). She was transferred to the surgical intensive care unit for closer monitoring and management with continuous pulse oximetry and initiation of heparin drip while bridging to therapeutic warfarin dosing. On postoperative day 4, the patient was found unresponsive with pulseless electrical activity (PEA). Advanced cardiac life support was immediately initiated. After 38 minutes of resuscitation, compressions were discontinued and death was pronounced.

Autopsy was performed, revealing the cause of death to be complications of multi-organ system involvement by

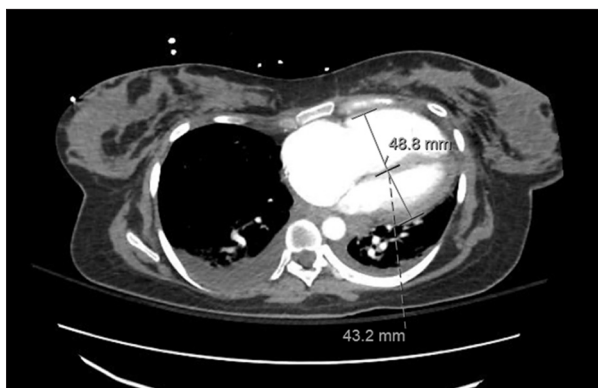


Figure 2. CT chest with prominence of the right ventricle when compared to the left ventricle, measuring 4.9 cm and 4.3 cm, respectively

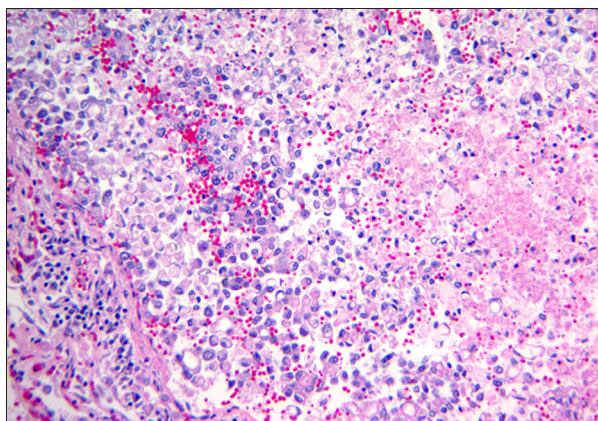


Figure 3. Higher magnification demonstrates the signet ring cell appearance of the tumor cells. Necrosis is also present (right side of the image) (H&E, 200 \times).

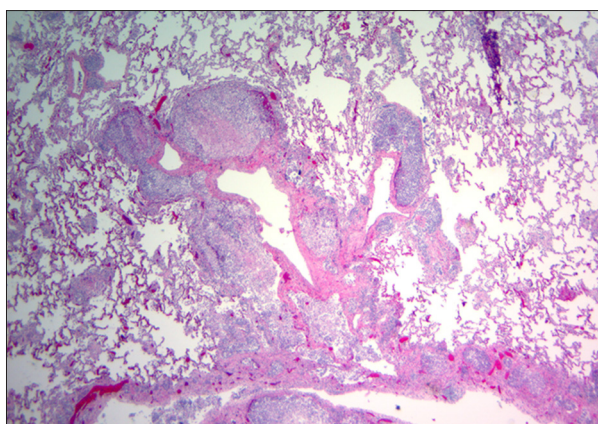


Figure 4. Lymphangitic spread of signet ring cell carcinoma in the lung (H&E stain, 20 \times).

adenocarcinoma with signet ring cell features (Figure 3). We discovered adenocarcinoma with signet ring cell features involving lymph-vascular spaces (lymphangitic carcinomatosis), as well as multiple small thrombi of all lobes of the lung, and

mediastinal/hilar lymphadenopathy involved by metastatic adenocarcinoma (Figure 4). The right ovary was also enlarged at 6.3 cm with a 4-cm right ovarian mass involved with adenocarcinoma with signet ring cell features. The vertebral bone marrow and spleen were also extensively involved. The primary site of cancer could not be definitively identified, although a gastric primary site was thought to be the most likely source given that gastric adenocarcinoma accounts for 96% of signet ring cell carcinomas.

Discussion

A literature search was undertaken by our research librarian using the search engines of PubMed and Web of Science. The search terms used included “lymphangitic OR lymphangitis AND carcinomatosis” AND “pregnancy”. The search was limited to articles in English and there was no limit on the years searched. Two authors (DDW and JRW) independently reviewed the abstracts and citations from the literature search. Inclusion criteria included any article that discussed lymphangitic carcinomatosis and its diagnosis or management in pregnancy. Only 1 case of metastatic lymphangitic carcinomatosis in pregnancy was found in the literature search [5].

Pulmonary lymphangitic carcinomatosis (PLC), defined as the spread of tumor cells throughout the lymphatic system of the lungs, occurs in 6–8% of patients with pulmonary metastases and is considered a rare end-stage manifestation of malignancy that carries a poor prognosis. The most common primary sites are the stomach, breast, lung, pancreas, colon, and prostate, with 80% being adenocarcinomas. Tumor cells are theorized to invade lymphatic vessels, likely through diaphragm and pleural surfaces, or spread from hilar lymph nodes, leading to obstruction of these vessels. As described in this case, patients with PLC often present with chief complaints of shortness of breath and pleuritic chest pain. Cough is another common presenting symptom. Without early recognition, complications of PLC, including pulmonary emboli, pulmonary hypertension, or cor pulmonale, can result in increased morbidity and mortality. Symptoms characteristic of the primary site of cancer are often absent [6–9].

This patient’s history of systemic lupus erythematosus (SLE) complicated the clinical picture, making a definitive diagnosis even more challenging, as most patients with SLE show some sign of involvement of the lungs, pulmonary vasculature, pleura, and/or diaphragm during the course of their disease. Pleural involvement is common in SLE and may cause chest pain. Patients also may report cough and/or dyspnea. Respiratory symptoms must also be distinguished from infection, particularly if the patient is on immunosuppressive therapy or in an immunocompromised state, as is the case with

pregnancy. Additionally, maternal complications of preeclampsia may include pulmonary edema, acute respiratory distress syndrome, and coagulopathy, which are all more likely to occur in the presence of pre-existing medical disorders such as SLE.

Imaging, including chest radiography and computed tomography (CT), in patients with PLC may be normal or have non-specific findings. Grossly, lung parenchyma appear normal on imaging [6]. More subtle findings due to extensive infiltration of lymphatic vessels with tumor cells include bronchovascular and interlobular thickening. Pleural effusions and hilar or mediastinal lymphadenopathy are other possible, although nonspecific, findings [6,9,10]. In this case, the initial CT chest demonstrated mediastinal and hilar lymphadenopathy with bilateral ground-glass changes and bronchovascular nodular changes. Chest radiography was also performed with no acute cardiopulmonary changes observed. Due to the inability to rule out infection, the patient was started on antibiotics, with no subsequent clinical improvement, making an underlying infection less likely to be the etiology of this patient's symptomatology.

Confirmatory diagnosis of PLC requires a histopathologic specimen through biopsy and is often not diagnosed until post-mortem at the time of autopsy [6,8]. This diagnostic delay is presumptively due to nonspecific symptomatology and radiographic findings, as well as a low initial suspicion for malignancy. In this case, there was no personal or family history of malignancy that would have raised the clinical suspicion for PLC and prompting lung biopsy. Due to these factors, along with the extent of metastatic disease seen with lymphangitic carcinomatosis, prognosis is generally poor [6,7]. In a systematic review and meta-analysis of case reports by Klimek, PLC can be the first manifestation of primary occult neoplasm,

occurring at any age, with approximately half of patients dying within 2 months of their first respiratory symptoms [11]. This is consistent with findings by Dennstedt et al., who reported that the diagnosis of primary gastric tumor with PLC was only made at autopsy in 4 of 6 patients; the patients included in this study had an average age of 26 and mean survival time of 22 days after initial hospital admission [12]. Additionally, gastric adenocarcinoma with signet ring cell histology is considered a poor prognostic indicator [6,7].

Conclusions

Diagnosis of cancer in pregnancy is often delayed as many symptoms of malignancy are nonspecific and common during pregnancy, including nausea/vomiting, dyspepsia, epigastric pain, abdominal pain, shortness of breath, breast changes, and fatigue [3]. In summary, the differential diagnosis for this patient was broad and included infection, lupus flare, heart failure, pulmonary embolism, preeclampsia, and malignancy. This may be one of the few cases of maternal death in which death was both unpredictable, unpreventable, and unavoidable.

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Conflicts of interest

None.

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