



Gastroesophageal Cancer During Pregnancy: a Case Report and Review of the Literature

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Introduction

Incidence of cancer during pregnancy is likely increased nowadays in developed societies and clinical practice due to women's increasing trend toward late childbirth [1]. While cancer develops in approximately 1 to 2 per 1000 pregnant women, the diagnosis of esophageal or gastric cancer during pregnancy or the lactation period is very rare, accounting for only 0.026 to 0.1% of all pregnancies [2]. Gastroesophageal junction (GEJ) cancer diagnosis during pregnancy is usually delayed due to low index of suspicion for having a malignant disease at a young age. Symptoms such as abdominal pain, nausea, vomiting, and fatigue can be mistaken as part of physiologic gestational symptoms and anemia as a laboratory finding. Additionally, this group of patients has some distinct features that may affect disease course such as being of young age, female gender, mostly being diagnosed at advanced stage, having a passive attitude toward treatment due to concerns about fetal health, and increased treatment challenges during pregnancy [3]. Early diagnosis allows appropriate management with a multidisciplinary approach. Contemporary

evidence suggest that chemotherapy can safely be given starting at 12 to 14 weeks of gestational age and radiotherapy of upper body parts, with adequate shielding, is expected to be safe during the first and second trimesters of pregnancy if the tumor is located sufficiently far from the fetus [4]. Low-risk surgery during pregnancy is feasible in all trimesters of pregnancy [5, 6].

Here, we report a case of gastroesophageal cancer diagnosed during pregnancy, the multidisciplinary management, and update of the literature. We also conducted a search on PubMed using “gastric cancer” AND “pregnancy,” and “gastroesophageal cancer” AND “pregnancy” as keywords beginning 1998 to 2017. Hits were carefully examined and two publications excluded as duplicate.

Case Report

A 28-year-old gravida: 2 para: 1, white female presented to her local emergency room with increased chest pain. She was 25 weeks pregnant at the time of her emergency room visit. She reported history of gastroesophageal reflux disease since age 15. She also reported worsening dysphagia for at least 3 months prior to presentation accompanied by weight loss of about 50 pounds (22.7 kg) over the last 10 months; nevertheless, she attributed the weight loss to increase in physical activity. During her emergency room visit, she was found to be tachycardic with shortness of breath and anemic with a hemoglobin of 8.1 g/dl. A computer tomography (CT) of the chest was done to rule out pulmonary embolism (PE). CT did not reveal a PE; however, it uncovered a distal esophageal mass. The patient subsequently underwent an upper endoscopy, which revealed a large obstructive ulcerated mass located adjacent to the gastroesophageal junction with suggestion of possible underlying Barrett's esophagus highly suspicious for malignancy, with biopsies positive for adenocarcinoma. She was noted to have a drop in her hemoglobin to 7 g/dl and she received blood transfusion. Due to concerns of active bleeding,

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she was transferred to a tertiary center for higher level of care. Upon arrival, the patient was hemodynamically stable (BP 136/64 mmHg, pulse 90 and respiration 18 per minute, temperature 97.7 °F, and SpO₂ 99%). She was well developed, with a BMI of 41.95 kg/m². She was not in acute distress. Proton pump inhibitor drip was initiated with subsequent stabilization of her hemoglobin. During admission, the patient was evaluated by high-risk obstetrics and a Doppler fetal monitor determined normal fetal heartbeats. The patient had further staging with magnetic resonance (MRI) without contrast that confirmed the GEJ mass but no abdominal metastases and a partially visualized intrauterine pregnancy (Figs. 1 and 2).

The initial CT of the chest was reviewed in our institution and did not reveal any metastatic disease. Further staging with upper endoscopic ultrasound (EUS) was performed revealing a partially obstructing malignant esophageal tumor involving the GEJ at 26–37 cm from the incisors, consistent with uT3N0, with representing biopsies confirming invasive moderately differentiated adenocarcinoma without nodal involvement. Her case was discussed in multidisciplinary tumor board and recommendations were to initiate systemic chemotherapy, followed by chemoradiation after delivery and subsequent surgery. The patient was discharged from the hospital in good condition without any further drop in her hemoglobin with plans to initiate chemotherapy as an outpatient. She received four doses of modified FOLFOX (biweekly oxaliplatin 85 mg/m² over 2 h (leucovorin was omitted) and fluorouracil 400 mg/m²/day over 15 min followed by fluorouracil 2000 mg/m²/day IV over 46 h). The patient had an uneventful vaginal delivery of a healthy boy, 2449 g, at 36 weeks of gestation. A positron emission tomography and computed

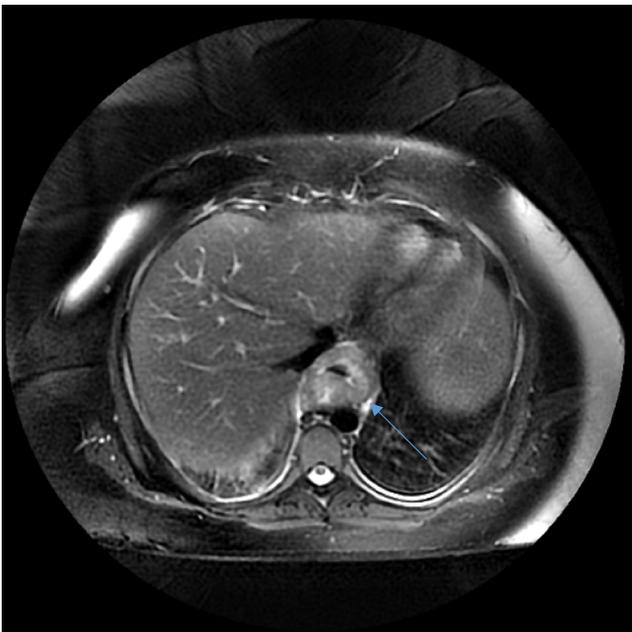


Fig. 1 Axial non-contrast T2-weighted image showing the GEJ tumor

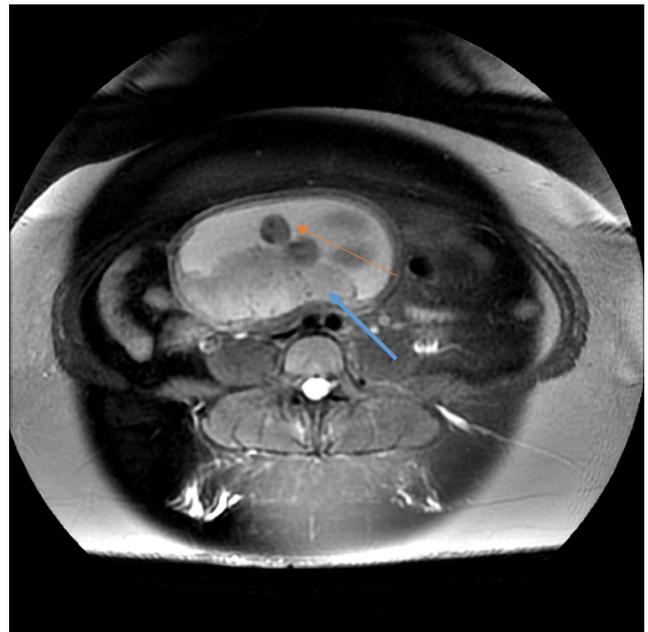


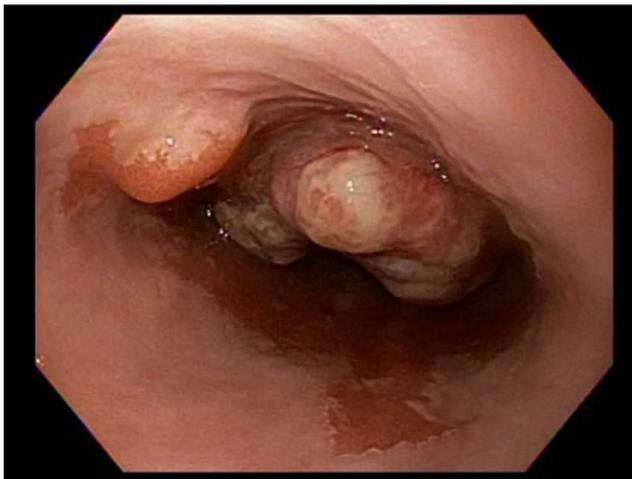
Fig. 2 Axial non-contrast T2-weighted image of the pregnancy. The blue arrow points out the placenta and the orange arrow points out the fetus

tomography (PET CT) performed after 2 weeks of delivery did show a concentric thickening of the mid and distal esophagus approximately 8 cm in length with associated standardized uptake value (SUV) of 24.7. The mass was grossly similar in anatomic appearance compared to initial CT at diagnosis and interpreted as stable disease without metastasis. She subsequently received chemoradiotherapy for a total of 5.5 weeks with weekly oxaliplatin and daily fluorouracil (from Monday thru Friday) and a total of 54 Gy of radiation divided into 28 fractions. After 5 weeks of treatment completion, a restaging of PET CT did show good response with decrease of FDG avidity of the tumor from 24.7 to 6.6 SUV. A restaging EGD showed 5-mm nodularity at 27–28 cm and nodular scar in the distal esophagus with focal ulceration at 35 cm (Fig. 3).

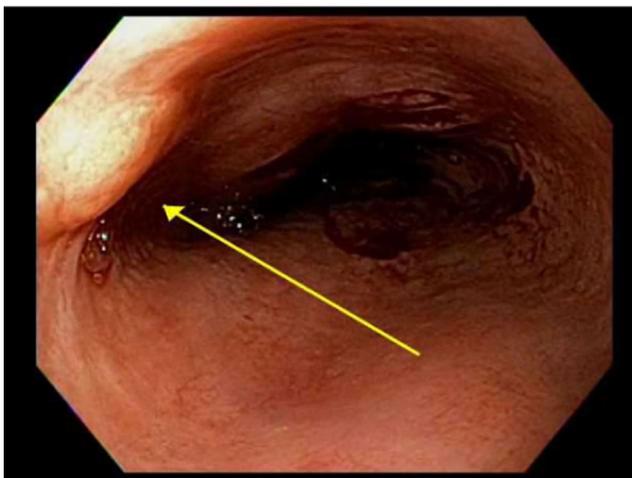
Representative biopsies of esophagus were negative for malignancy.

The patient underwent a standard Ivor Lewis esophagectomy, performed via upper midline abdominal incision and posterior muscle-sparing thoracotomy. Chemical pyloromyotomy was performed, as well as thoracic duct ligation and placement of a feeding jejunostomy. She was managed according to a protocolized-enhanced recovery pathway, and she did well postoperatively, with no complications. Contrast esophagram on postoperative day 7 revealed absence of leak, and oral intake was initiated prior to hospital discharge.

Surgical pathology revealed a single focus of invasive moderately differentiated adenocarcinoma in a setting of Barrett's mucosa with low-grade dysplasia. Evaluation of her specimen revealed less than 1% viable tumor in an area



Pre-treatment



3 focal nodularity ~27-28cm

Post treatment

Fig. 3 Pre- and posttreatment appearance of tumor

of 0.3 cm at greatest dimension within 6.8 cm tumor bed, with epicenter 1.2 cm proximal to gastroesophageal junction invading esophageal submucosa. Thirty lymph nodes were examined; all of them were negative for malignancy. The final pathological staging was ypT1bN0, according to *AJCC 7th Edition*, 2010.

Our patient is currently with no evidence of disease carrying on a busy life with two healthy children.

Discussion

Gastroesophageal cancer during gestation is an extremely uncommon condition and can be difficult to diagnose by health

care professionals due to tendency to interpret the constellation of symptoms as part of pregnancy. Our search revealed that over the last 20 years, only five cases of esophageal or GEJ cancer and 36 cases of gastric cancer during pregnancy have been reported in the literature. Characteristics of presentation and treatment of all five pregnancy-associated esophageal cancer patients in literature are summarized in Table 1 [7–42]. Nine patients (22%) were diagnosed at an early stage. The most frequent complaint was weight loss. Ten (24%) patients had abdominal pain (including low abdominal/back pain). Eight (20%) patients presented with epigastric pain, five (12%) with pre-eclampsia, four with persistent vomiting, and three with dysphagia. Other presenting complaints were lymph node enlargement, hematemesis, dyspnea, ascites, and gastric perforation.

A study by Ueo et al. reviewed a total of 61 Japanese gastric cancer cases diagnosed during pregnancy and reported that about 97% of them were at an advanced stage. Based on their experience and literature review, Ueo et al. also recommended a practical guideline suggesting consideration of termination of pregnancy before 22 weeks of gestation followed by treatment. If cancer is diagnosed after 28 weeks, treatment should be applied after early delivery [2, 43]. However, management for a cancer diagnosed from 22 to 28 weeks of gestation is not clear. Treatment of early gastroesophageal cancer may be deferred to ensure fetal maturation until 28 weeks; with advanced perinatal management, curative surgery may be a feasible option [38].

In order to determine the impact of pregnancy, age, and female sex, Jaspers et al. analyzed 31 gastric cancer cases published from Western institutions. This study included cases diagnosed during pregnancy compared to young patients (< 40 years) without pregnancy. All of the cases from Western institutions were advanced stage, and there were minor clinicopathologic differences between young patients without pregnancy, concluding that there was no influence of pregnancy, young age, and/or female sex on the prognosis of gastric cancer. However, a small number of patients with better survival rates in Japanese patients reported by Maeta [44] and Furukawa [45] let the authors outline the advantage of early detection and curative surgery, and the recommendation of diagnostic procedures like endoscopy for cases especially accompanied with weight loss and persistent epigastric complaints in the second trimester [46]. Sakamoto et al. analyzed 137 gastric cancer cases diagnosed during pregnancy published by Japanese institutions collected until 2007. The vast majority of patients, 118 of 124 (95.2%), were of advanced stage, and the 1- and 2-year survival rates were 18 and 15.1%, respectively. Considering the last 20 years, between 1988 and 2007, the 1- and 2-year survival rates improved to 37 and 31.8%, respectively, due to increase in diagnosis of early-stage cancer together with endorsement of endoscopy

Table 1 Clinical characteristics, treatments, and outcomes of five cases from the literature

Reference	Age	GA at Dx	Presenting symptom	Tumor location	Histology	Stage	Treatment
Sharma et al. [7]	36	29w	Hematemesis	GEJ	Adenocarcinoma	IV	Supportive care
Al-Githmi et al. [8]	29	29w	Dysphagia	Lower esophagus	Squamous cell carcinoma	IV	Supportive care
Jain et al. [9]	27	26w	Dysphagia	Upper esophagus	Squamous cell carcinoma	Local recurrence	Pall-CTx (taxane, platin)
Sahin et al. [10]	26	27w	Dysphagia	Middle esophagus	Squamous cell carcinoma	III	Esophagectomy
Akdemir et al. [11]	39	28w	Dysphagia	Lower esophagus	Squamous cell carcinoma	III	Refused NeoAdj-CTx

GA, gestational age; Pall-CTx, palliative chemotherapy; Adj-CTx, adjuvant chemotherapy; NeoAdj-CTx, neoadjuvant chemotherapy; UK, unknown; GEJ, gastroesophageal junction; w, week

since the 1980s. They also pointed out an increase in the number of patients over 30 years old or older in the most recent years [2].

Consistent findings of female predominance and aggressive tumor biology at reproductive ages raise the question of hormonal and reproductive effects on gastric cancer disease course. Two researchers from Japan observed a higher frequency of poorly differentiated adenocarcinomas with scirrhous growth and peritoneal metastasis and accelerated gastric cancer growth in pregnant patients suggesting estrogen may promote cancer growth [44, 45], whereas some other studies argue a protective role [47]. The placental growth factor, a member of vascular endothelial growth factor family, is expressed only in placenta and it is shown to be associated with poor survival and TNM stages in gastric cancer [48].

Estrogen production increases continually in pregnant women reaching more than 1000-fold [49]. Perspective from parity may clarify conflicting data if pregnancy has a role gastric cancer. Meta-analysis of 10 prospective cohort studies (5 from Europe, 4 Asia, 1 USA) published between 2000 and 2012, that included 6624 gastric cancer cases and 5,559,695 non-cases, did not find association between parity and development of gastric cancer. Conversely, the result marginally suggests that parity might help protect against the development of gastric cancer [50]. To help further delineate and understand if sex hormones and pregnancy affect the gastric cancer disease course, Song et al. from South Korea compared a cohort of 20 patients with pregnancy-related gastric cancer to age, sex, and stage with a matched control cohort of 39 gastric cancer patients without pregnancy referred to tertiary referral hospital between 1991 and 2012. The study evaluated prognostic clinicopathologic factors as expression of E-cadherin, estrogen receptor (ER), progesterone receptor (PR), epidermal growth factor receptor (EGFR), and human epidermal growth factor receptor 2 (HER2) by using

immunohistochemistry (IHC) and fibroblast growth factor receptor 2 (FGFR2) amplification by using fluorescence in situ hybridization (FISH) between cases and controls. This study showed that patients with pregnancy-related gastric cancer had a worse prognosis compared to that of the whole group (case plus control) if their tumor stage was advanced (stage IV vs. stages I, II, III), diagnosed in the third trimester pointing out that symptoms of gastric cancer frequently overlap with pregnancy-related symptoms such as gastric discomfort and hyperemesis that may delay diagnosis. However, there was no difference for the median time from the onset of symptoms to diagnosis between cases compared to controls (77.4 [IQR, 30 to 142.5 days] days for cases vs. 66 [IQR, 28 to 208 days] days, respectively; $p = 0.242$). The median survival time of pregnancy-related gastric cancer patients who underwent gastrectomy was 32.4 months (IQR, 21.8 to 76 months) compared with 6.2 months (IQR, 1.0 to 7.0 months) for those who received palliative chemotherapy and 2.1 months (IQR, 1.0 to 13.5 months) for those who were given the best supportive care only emphasizing the importance of diagnosing at an early stage. The IHC or FISH results did not show a difference between case and control groups. The median time from diagnosis to treatment was longer in the case group than that in the control group (21 vs. 7 days, respectively; $p = 0.021$). This may reflect the fact that expecting mothers tend to hesitate when faced with the need for immediate treatment because the surgery or chemotherapy could harm the fetus. The authors found that detection at an early stage and curative resection were the most important and effective approaches in gastric cancers during pregnancy [3]. Accumulating data convincingly shows that younger patients, including pregnancy-related, with gastric cancer could have an improved prognosis if they undergo surgery and pregnancy-related disease course has mainly the same features as other patients at a young age cohort. Also, patients that present with advanced stage at

diagnosis likely had gastric malignancy before conception, while if pregnancy itself boosts cancer growth remains elucidated and deserves more investigation.

Another risk factor that needs special attention is obesity, an increasingly serious health issue for patients in nearly all Western countries. Obesity is related with higher incidence of GERD. Barrett's esophagus, a complication of GERD, predisposes patients to esophageal adenocarcinoma. The annual risk of esophageal cancer is approximately 0.25% for patients without dysplasia and 6% for patients with high-grade dysplasia [51, 52]. The American Society of Gastrointestinal Endoscopy (ASGE) suggests that endoscopic screening for BE may be considered for selected individuals with multiple risk factors like long history of GERD (more than 5 years), high BMI ($> 25 \text{ kg/m}^2$), and white race [53]. For patients with Barrett's esophagus without dysplasia, endoscopic surveillance at intervals of 3 to 5 years is recommended, and GERD is treated as it is for patients without Barrett's esophagus (BE) [52]. Endoscopic eradication therapy is the treatment of choice for high-grade dysplasia and is an option for low-grade dysplasia.

Although nausea and vomiting are the most frequent symptoms of pregnancy, 90% of cases improve by the 16th week of gestation. Persistent symptoms with weight loss require prompt assessment in the second trimester. The ASGE recommends endoscopy in pregnant women carried out only when there is a strong indication and to be postponed to the second trimester, whenever possible [54].

Staging examinations for cancer during pregnancy should be as comprehensive as that for non-pregnant patients. If radiographic procedures are deemed necessary, dose exposure of ionizing radiation to the fetus needs to be justified to make sure that they should be "as low as reasonably achievable (ALARA)": a maximum cumulative dose of 50 mGy was determined by the American Association of Physicists in Medicine (AAPM) [55, 56]. Chest X-ray, with adequate radioprotection, ultrasonography, and MRI are preferred staging modalities. Gadolinium-based agents, considered as a category C drug, should be avoided in pregnancy [57]. When it is deemed feasible, the cure of patients should remain the top priority together with navigating the pregnancy as high risk, and whenever possible, a term delivery should be aimed for [58]. Chemotherapy administration should also be established during pregnancy. The use of chemotherapy during the first 12 weeks is discouraged and termination of pregnancy would need to be discussed with patients requiring chemotherapy at this period. The first 2 weeks of gestation, and following 10 weeks, "organogenesis period," are most vulnerable periods associated with malformations as high as 20% [59]. After the second trimester, the use of chemotherapy is relatively safe; however, a cohort study comparing 129 children whose mothers had cancer (96 children exposed to chemotherapy, 11 to radiotherapy, and 13 to surgery) with a matching

number control group showed numerically increased small for gestational age (22.0 vs. 15.2%) and normal cognitive development [60]. The experience with breast cancer is the most frequent cancer in pregnancy, in particular with anthracycline-containing combinations such as 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) and 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) can safely be given after first trimester [61]. Methotrexate was used for induction of abortion and should be avoided during pregnancy [62]. Taxane and platinum-containing regimens, which are standard of care for gynecological regimens, used in 20 patients with epithelial ovarian cancer during pregnancy resulted without significant consequences [63]. Carboplatin should be preferred over cisplatin; hence, cisplatin was related with more fetal adverse events [64]. Few reports on taxanes, mainly paclitaxel, did not describe any fetal anomalies [65]. Two patients were treated with FOLFOX6 regimen in the second trimester for colorectal cancer during pregnancy: one patient delivered electively on the 31st week a baby girl with hypothyroidism [63]. Trastuzumab or any other HER2-targeted agents is contraindicated throughout the pregnancy, and patients with HER2⁺ disease should be given these agents after delivery.

Chemotherapy followed by radiation and surgery is currently the recommended treatment for localized ($>T1bN0M0$) esophageal cancer and GEJ cancers [66]. About 25% achieve pathological complete response and those responders have improved survival and decreased the risk for recurrences [67, 68]. Our patient who had BE (likely her premalignant condition), as noted on the initial biopsy, was found to have localized GEJ cancer during her second trimester of pregnancy. Although her disease was complicated by the high-risk pregnancy, as the second trimester is secure for chemotherapy but not for radiotherapy, her treatment plan conceptualized with intent to cure starting with preoperative chemotherapy followed by chemoradiotherapy, and finally, surgery. The treatment resulted in delivery of a healthy baby and curative surgery with near-complete pathologic response.

Conclusion

Protracted digestive symptoms and weight loss in the second trimester require prompt assessment. Young, pregnant patients with underlying obesity and GERD should be closely asked about symptoms of dysphagia or heartburn that do not subside and should raise a red flag and consideration for an upper endoscopy. Curative surgery for early cancer should be pursued in advanced facilities with experience in perinatal management. Chemotherapy is safe during the second and third trimesters and all efforts should be made to treat the mother and to have a term delivery.

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