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Anal Squamous Cell Carcinoma in Pregnancy: A Case Report

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1. Abstract

1.1. Introduction

A diagnosis of anal cancer during pregnancy is rare, and management often falls outside of guidelines. This report presents a case of anal squamous cell carcinoma diagnosed during a high-risk pregnancy in a patient with multiple previous pregnancy losses.

1.2. Case Description

A 39-year-old patient presented with a painful rectal mass. Anoscopy demonstrated a firm right-sided anal canal mass with central ulceration, extending the length of the anal sphincter. Biopsy confirmed poorly differentiated squamous cell carcinoma. During workup, the patient was found to be 10 weeks pregnant. She had multiple prior pregnancy losses and chose to continue this pregnancy. Staging PET MRI showed a 2.6 cm mid-anal canal mass involving the internal anal sphincter and abutting the external sphincter and posterior vagina (T2), with suspicious bilateral inguinal and mesorectal nodes (N1a) without distant metastases. A diverting loop ileostomy was constructed for palliation of pain and incontinence. Carboplatin and paclitaxel were administered during pregnancy. Following delivery by Cesarean section at 34 weeks, and 7.5 week recovery, she underwent chemoradiation with concurrent fluorouracil and mitomycin. Ileostomy was closed eight months after completion of treatment. Eighteen months after completion of therapy there was no evidence of persistent or recurrent disease.

1.3. Conclusion

Treatment of anal squamous cell carcinoma in pregnant patients requires multidisciplinary care and must be adapted to current guidelines and stage of pregnancy. Chemotherapy after the first trimester, and chemoradiotherapy after delivery worked well for this patient.

2. Introduction

It is estimated that there will be more than 10,000 new cases of anal cancer in United States in 2024, according to Surveillance, Epidemiology, and End Result Research Program (SEER) [1]. Risk factors for anal squamous cell carcinoma (aSCC) include female sex, immunosuppressive situations such as Human Immunodeficiency Viral (HIV) infection or solid organ transplant, and vulvar dysplasia or carcinoma. aSCC often develops from high-risk Human Papillomavirus (HPV)-associated dysplasia. However, aSCC can develop outside of HPV infection and in such cases is associated with a worse prognosis [2-4]. Standard-of-care treatment of localized aSCC involves chemoradiation with concurrent mitomycin C and fluorouracil; surgery is reserved for aSCC that persists or recurs after chemoradiation [5]. Also rare, is a diagnosis of cancer during pregnancy, which occurs in around 1 in 1,000 pregnancies [6]. Pregnancy-associated cancer (PAC) is defined as a malignant neoplasm that is diagnosed during pregnancy and up to 1 year postpartum [7]. Cottreau et al found that only 29% of PAC patients were diagnosed during pregnancy, and the remaining 71% were diagnosed during the first year postpartum [8]. PAC requires complex multidisciplinary decision making, involving medical and surgical oncology specialists, Maternal-Fetal Medicine specialists, pathologists, and radiologists. Always at the center of decision making is the patient. Guidance can be challenging, especially for rare cancers in uncommon situations such as PAC. Options include standard oncologic management during pregnancy, modified oncologic management during pregnancy, deferral of oncologic management until after completion or pregnancy, or termination of pregnancy and standard oncologic management. The type, timing and dosing of chemotherapy must be cautiously considered in a pregnant

patient, and initiation of chemotherapy is often delayed until after the first trimester to minimize teratogenic toxicities. Pelvic radiotherapy is contraindicated during pregnancy and should be postponed until after delivery due its association with fetal death, malformations, and growth abnormalities [9]. Surgery during pregnancy is not contraindicated, but special considerations for anesthetic safety, surgical approach, and risks particularly of abdominopelvic surgery in pregnancy must be considered. This report presents a case of anal squamous cell carcinoma diagnosed in the first trimester with successful pregnancy and oncologic outcomes after treatment with chemotherapy during pregnancy followed by chemoradiation in the postpartum period.

3. Patient Information

A 39-year-old G9P2342 female initially presented with a hard, painful nodule of several months' duration on the right side of her anus. There was no history of prior bleeding or drainage, no previous colonoscopy, and no family history of colorectal cancer. The patient was negative for HIV, cervical dysplasia, and HPV infection. She had been vaccinated for HPV with the quadrivalent Human Papillomavirus (4vHPV) immunization 16 years prior. Other notable medical issues were attention deficiency hyperactivity disorder (ADHD), hypothyroidism after treatment of Graves' disease with radioactive iodine ablation, and tobacco use. Obstetrical history was significant for two prior term vaginal deliveries, three first trimester miscarriages, two second trimester losses, and 25-week medically indicated delivery via cesarean section due to conjoined twin gestation complicated by congenital diaphragmatic hernia and neonatal demises. Her first term delivery was complicated by pruritic urticarial papules, preeclampsia, and gestational diabetes mellitus; second term delivery was complicated by gestational diabetes. She also had a history of placental abruption with fetal demise resulting in one of her second trimester losses. She had no prior abdominopelvic operations other than one prior cesarean delivery. She presented to her general practitioner with concerns of "painful hemorrhoids" that started a few months prior, and on exam a firm mass was found on the right side of the anal canal. The mass was biopsied in the operating room and found to be squamous cell carcinoma. On preoperative lab work for the biopsy, she was found to be pregnant. Ultrasound confirmed 10-week pregnancy. Initial Magnetic Resonance Imaging (MRI) of pelvis showed a 2.6 cm mass-like process in the right side of the anus extending through the internal anal sphincter to the intersphincteric space (Figure 1). Subsequent PET-MRI also identified suspicious mesorectal and bilateral inguinal lymph nodes and fistulization of the mass to the gluteal cleft. The mass abutted but did not invade the external anal sphincter and vagina and there was no distant metastatic disease (cT2N1aM0, Stage IIb). She was referred to our center for advanced care of her cancer and high-risk pregnancy and was cared for by a multidisciplinary team including Medical Oncology, Radiation Oncology, Colorectal surgery, Maternal-Fetal Medicine. After the biopsy, she developed a fistula that leaked stool and required antibiotics for purulent fistula drainage. She could not tolerate an exam in the clinic, and given the purulent discharge, was taken for exam under anesthesia. Exam in the operating room revealed a firm right-sided anal canal mass extending the length of the anal sphincter and with central ulceration. The anorectal mucosa and sphincters on the right posterolateral quadrant were completely eroded by cancer. There was a cancer lined cavity filled with stool and pus that was opened into the rectum to allow for drainage (Figure 2). The tumor did not involve the vagina. Pathology from incisional biopsy showed moderately to poorly differentiated squamous cell carcinoma with positive p16 staining indicating HPV infection. After extensive counseling with her multidisciplinary care team, the patient decided to continue the pregnancy and undergo oncologic treatment. Her treatment plan was thus carefully crafted to safeguard her pregnancy and ensure the best possible oncologic outcomes. It was recommended to her to start with systemic therapy with carboplatin (AUC 5 on day 1 every 28 days) and paclitaxel (80 mg/m2 on days 1, 8, and 15 every 28 days) in the second trimester and continue systemic therapy until about 4 weeks prior to delivery, which was tentatively planned via cesarean between 34-37 weeks gestation, and proceed to standard chemoradiation with concurrent mitomycin C and fluorouracil in a month following delivery. Prior to starting chemotherapy, she was hospitalized with relentless pelvic pain and underwent a diverting loop ileostomy for symptom management. At 19 weeks gestation, she started chemotherapy with carboplatin and paclitaxel. PET-MRI after 2 cycles of chemotherapy, at 26 weeks gestation, showed overall stable disease but new soft tissue thickening in the right ischioanal space suspicious for disease progression. PET-MRI was therefore repeated after her 3rd cycle of chemotherapy, which demonstrated increased intensity of asymmetric FDG activity along the right aspect of the anal canal. Due to concerns for local disease progression the last cycle of chemotherapy was canceled, and she underwent a planned repeat cesarean delivery at 34 weeks gestation. A viable male neonate weighing 2.4 kg was delivered with APGARs of 5 and 9 at 1 and 5 minutes respectively. The neonate was cared for in the NICU. After delivery, incidental fetal spina bifida was diagnosed and treated via surgical repair. The baby was fed on donor breast milk and formula, while the patient pumped her breast milk and disposed of it to continue lactation until she completed chemotherapy. PET-MRI 4 weeks post-partum showed interval increase in the size of the anal mass to 3 cm but otherwise stable findings. Initiation of chemoradiation was delayed to 7.5 weeks post-partum to accommodate post cesarean recovery, care needs of the child, and to allow time for the post-pregnancy uterus to return to non-pregnant size for stable and reproducible anatomy with proton chemoradiotherapy. Curative-intent chemoradiotherapy regimen, 53.2 Gy in 28 fractions with concurrent mitomycin C (10 mg/m2 on days 1 and 29) and fluorouracil (1000 mg/m2 on days 1-4 and days 29-32). Proton therapy was utilized to allow better sparing of normal tissues from radiation exposure thereby reducing the risk of side

effects and theoretical risk of radiation-associated secondary malignancy. Unfortunately, patient developed chest pain on day 3 while receiving continuous fluorouracil infusion. Treatment was paused and she underwent extensive cardiovascular evaluation which did not reveal a clear etiology. Her chest pain resolved without further interventions. To minimize the risk of fluorouracil-related coronary vasospasm, it was decided to switch from fluorouracil infusion to fluorouracil bolus injection (400 mg/m2 weekly during chemoradiation) [10]. She also struggled with anticipated side effects from concurrent chemoradiation including fatigue, neutropenia, nausea, and radiation dermatitis, which all resolved after completion of therapy. Her anal pain improved with decreased drainage from the fistula. She developed a parastomal hernia which was uncomfortable. Three months after completion of chemoradiation, anorectal examination under anesthesia was performed and demonstrated some mild anal canal narrowing but no mass lesion. There was loss of the lower third of the internal sphincter and a portion of the external sphincter mechanism on the right posterior lateral aspect of the anal canal, but the proximal two thirds of the sphincter were intact circumferentially. Surveillance PET-MRI and CT scans of chest, abdomen and pelvis were performed 4 months after completing chemoradiation and showed near complete/complete response of anal cancer without evidence of metastatic disease. Surveillance CT scans 4 months later again demonstrated complete response. Patient then underwent diverting ileostomy reversal and parastomal hernia repair with mesh. She had reasonable functional outcomes without incontinence even with the anal sphincter defect and pelvic radiation. Fifteen months after definitive chemoradiation, patient reported symptoms concerning for a recurrent fistula. On exam under anesthesia, a small keyhole deformity of the right anterio-lateral aspect of the anal sphincter was found with a complete healing of the mucosa over the sphincter. Patient remains cancer free to date with the last surveillance exams performed 18 months after completion of chemoradiation.

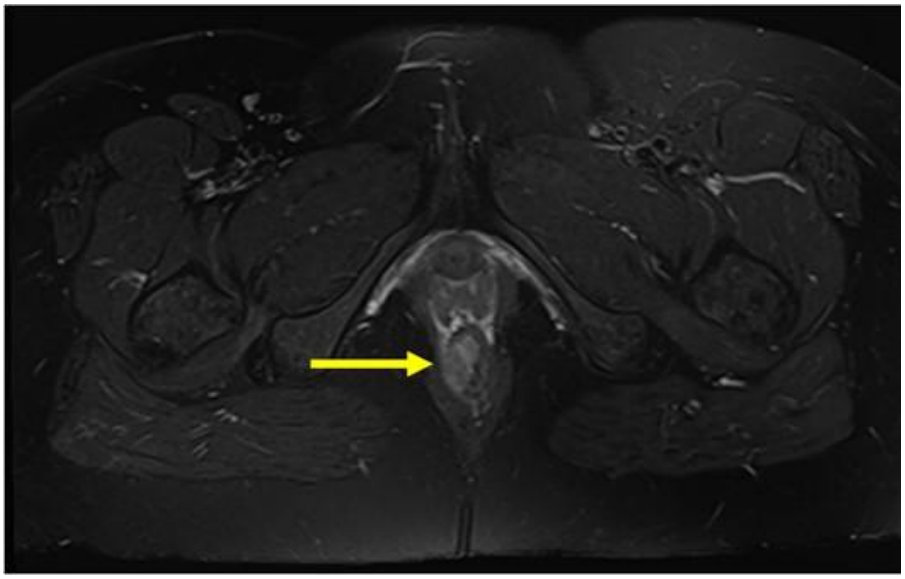

Figure 1: Magnetic Resonance Imaging (axial T2) of the pelvis before the treatment, yellow arrow indicating the tumor.

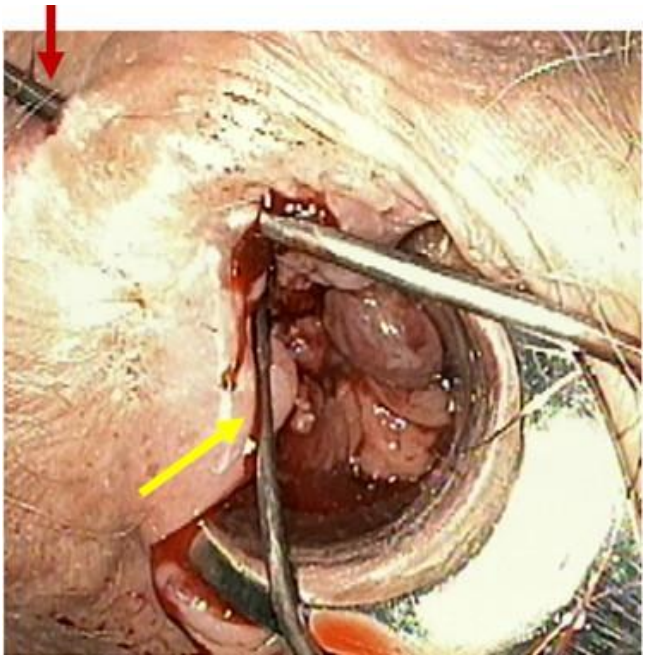

Figure 2: Pretreatment image showing a probe in the fistula tract (red arrow) and a probe into the large cavity (yellow arrow).

4. Discussion

Cancer diagnosed during pregnancy presents unique clinical challenges. Gastrointestinal cancers during pregnancy can be more challenging to detect as their symptoms may mimic common pregnancy-related changes, such as hemorrhoids or constipation, resulting in delayed diagnosis and advanced stage of disease at time of diagnosis. In addition, diagnostic delays may result from reluctance to perform invasive procedures or imaging studies due to concerns about fetal exposure. The dual consideration of maternal and fetal health further complicates decision making, requiring a careful balance between timely cancer treatment and minimizing the harm to the developing fetus. Regarding aSCC diagnosed during pregnancy, only one previously published case report exists [3]. It describes a case of 34-year-old 24-week pregnant patient with a history of HPV-associated cervical dysplasia (c-EIN III) and a diagnosis of stage IIIB aSCC (cT4N0M0), who underwent treatment with paclitaxel and carboplatin and delivered by cesarean section at 35 weeks gestation. The infant was healthy. In the postpartum period, imaging showed tumor progression and patient underwent chemoradiation with complete clinical response at three months. Patient experienced regrowth thereafter and received 5 cycles of nivolumab followed by abdominoperineal resection [3]. Despite the effectiveness of chemoradiotherapy (CRT) as the primary treatment of anal SCC, locoregional recurrence rates can be up to 35% [5,11]. Risk factors for cervical as well as anal malignancy are strongly associated with human papillomavirus (HPV) infection. Although in this case the patient had a negative cervical HPV test, and had been vaccinated against HPV, her anal cancer biopsy was p16-positive, which is a marker for HPV infection. Advanced imaging for cancer staging during pregnancy presents additional considerations. PET during pregnancy requires careful risk–benefit assessment, as the 18F-FDG radiotracer crosses the placenta, delivering a small dose of ionizing radiation to the fetus. Although reported fetal doses from pregnancy-adapted PET protocols are generally between 1–5 mGy-well below thresholds for deterministic effects-there remains a theoretical risk of carcinogenesis, particularly during organogenesis [12,13]. When PET is clinically justified, protocols should be adapted to minimize exposure, including strict justification of indication, lowering administered activity, ensuring maternal hydration, encouraging frequent bladder emptying, and using abdominal shielding and preferentially selecting PET/MRI over PET/CT when feasible, in accordance with the ALARA (As Low As Reasonably Achievable) principle and published dosimetry studies [14-17]. In the present case, PET-MRI was performed for staging, and pregnancy-specific safety measures were implemented. Although stage IIA anal squamous cell carcinoma is typically treated with chemoradiation, pregnancy precludes the use of pelvic radiation due to its potential harm to the fetus. The optimal treatment approach in pregnant patients with malignancy is to reduce tumor burden and improve maternal survival while carefully balancing the potential fetal risks associated with treatment. According to the American Society of Colon and Rectal Surgeons (ASCRS) [18] National Comprehensive Cancer Network (NCCN) [19], and European Society of Medical Oncology (ESMO) guidelines [20], the first-line systemic regimen when delivered concurrently with radiotherapy for aSCC is mitomycin C/and-fluorouracil. The international multicenter randomized control trial in advanced anal cancer (InterAAct) suggests that the combination of carboplatin and paclitaxel should be considered the standard of care, first-line therapy in patients with metastatic anal cancer [21]. Recently, the addition of retifanlimab to carboplatin and paclitaxel was approved by the Food and Drug Administration based on the phase 3 POD1UM-303/InterAACT 2 (NCT04472429) clinical trial demonstrating improved survival with the addition of an anti-PD-1 immune checkpoint inhibitor. However, treatment must be adapted to gestational age and fetal vulnerability in pregnant patients. ESMO guidelines on the treatment of gynecologic cancer in pregnancy state that chemotherapy is contraindicated during the first trimester due to the risk of teratogenicity and interference with organogenesis. After the 14th week of gestation, certain chemotherapeutic agents such as taxanes, platinum agents, anthracyclines, etoposide, and bleomycin are considered relatively safe with main fetal risks related to growth abnormalities. To minimize potential risks to both the mother and fetus, chemotherapy should generally be discontinued by the 37th week of gestation [22]. A meta-analysis by Yizuo Song et al. [23], reported in 2018, evaluated the use of platinum-based chemotherapy in pregnant patients with cervical cancer and found that in the majority of cohorts the newborns had appropriate fetal growth, normal APGAR (Appearance, Pulse, Grimace, Activity, and Respiration) scores, and were reported to be healthy at follow-up. Two rare adverse outcomes were reported: one case of retroperitoneal embryonal rhabdomyosarcoma at the age of 5 years old, and one case of acute myeloid leukemia diagnosed at 22 months [23]. In the case reported herein, the neonate had spina bifida requiring surgery. Regardless of apparent normal development at birth, neonates exposed to chemotherapy in utero should undergo a comprehensive postnatal evaluation, including hematologic assessment, liver and renal function tests, and cardiologic examination – especially if cardiotoxic agents were administered during pregnancy. If platinum-based agents were used, additional attention should be given to the infant's auditory function due to the risk of irreversible hearing loss [22]. Overall, maternal malignancy during pregnancy is not typically associated with poor perinatal outcomes, such as low-birth weight, fetal growth restrictions, intrauterine fetal death, or congenital malformations [24,25]. Maternal risks from chemotherapy are mainly related to known, common side effects of multi-agent cytotoxic regimens, including sepsis and cytopenias.

5. Conclusion

Anal cancer during pregnancy is extremely rare. Treatment decisions should be adapted to current guidelines and discussed by a multidisciplinary team. Concurrent chemoradiotherapy is the standard approach to localized aSCC. However, during

pregnancy, chemoradiotherapy is not safe. In both the present case and the previously reported case, patients received carboplatin and paclitaxel during pregnancy, which led to disease control, safely prolonging pregnancy with excellent neonatal outcomes. Neonatal outcomes included one healthy infant and one case of incidental spina bifida. Both patients had delay of initiation of chemoradiation after delivery with our patient having persistent complete response at 18 months and the other report of recurrence requiring APR (time of recurrence not reported). Drawing on these rare reports, as well as the treatment of other cancers during pregnancy, support the overall safety of a chemotherapy-delivery-chemoradiation approach to treatment of anal squamous cell cancer during pregnancy. This approach requires careful monitoring and coordinated multidisciplinary care to optimize maternal and fetal outcomes.

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