Small cell carcinoma of the cervix (SCCC) was first described in 1957 and represents 1%-3% of all cervical malignancies. SCCC is a unique member of the neuroendocrine group of cervical carcinomas and spreads very quickly during the early stages of the disease. As an aggressive tumor, SCCC usually leads to a fatal clinical outcome. The 5-year survival rates vary from 0%-30%, and long-term survival is only achieved in patients with very limited disease. Because the median age of SCCC patients is 42-44 years, pregnancy is extremely rare. The diagnosis of SCCC in pregnant women is more likely to occur at a later stage of the disease and the clinical course is frequently marked with metastatic disease and death. In this case report, we present the diagnosis and treatment of an SCCC patient in late pregnancy.

Case Report

A 25-year-old woman in the 32nd week of pregnancy presented with abnormal vaginal bleeding that had continuously occurred for 1 month. The patient was hospitalized at Qilu Hospital of Shandong University on May 2, 2010. On March 19, 2010, the patient presented with a small amount of vaginal bleeding without abdominalgia and was treated as an outpatient at another hospital. Without a gynecological examination, the patient was diagnosed with threatening abortion and was treated with abortion prevention drugs. On April 17, 2010, the patient presented with additional vaginal bleeding that was more excessive than typical menstruation; a histopathological examination of vaginal exfoliate tissue was performed at another hospital. A cervical biopsy revealed SCCC that was Syn(+)/CgA(-)/CK5/6(-). The patient was transferred to our hospital on May 2, 2010, and was diagnosed with SCCC by cervical biopsy. Upon gynecologic examination, the cervix exhibited an abnormal shape, retained a portion of the pelvic sidewall, and contained a cauliflower-like mass that was 10 cm in diameter. Rectal touch indicated that the mass had invaded the left pelvic cavity. The value of the HC2 test, which assesses the presence of HPV DNA from 13 different high-risk strains, was 2507.06 and markedly higher than the normal value for a negative patient (1.00). After a collaborative discussion with other gynecologists...
in our department, we concluded that this was a complex clinical scenario.

It is difficult to perform a Cesarean section concomitantly with a radical treatment plan. Therefore, our team decided to initiate an aggressive chemotherapeutic and radiation plan after performing a Cesarean section. Since the patient and her family wished to maintain the pregnancy, the Cesarean section was delayed until fetal lung maturation occurred by using dexamethasone intramuscular injection for the patients. The patient delivered a healthy, 3.9-pound male infant by elective Cesarean section on May 7, 2010. The neonate’s Apgar score at 1 minute and 5 minutes were 6 and 8, respectively, and the baby was transferred to the NICU for monitoring. The surface of the uterus was smooth, the adnexa uteri were normal, and the cervical canal was slightly larger than normal. A biopsy determined the presence of a poorly differentiated metastatic tumor.

After consent from the patient and her family, a radical hysterectomy was performed; the uterus and cervical stroma were excised, the pelvic lymph node was bilaterally dissected, and the para-aortic lymph node was biopsied. During the surgery, a metastatic mass measuring 3 × 2.5 × 2.5 cm in size was found in the left cervical stroma and the obturator lymph nodes were enlarged. The patient was subsequently diagnosed with stage Ila cervical cancer. Thirteen days after the surgery, there were no detectable cancer cells identified in the ascites sample. On May 21, a computed tomography (CT) scan showed metastatic liver infiltration (Image 1). The patient experienced bloating on May 23 and was treated to alleviate water retention. Cisplatin (50 mg) was also administered by peritoneal perfusion on the same day. On May 25, the patient was transferred to another hospital for treatment as requested. The patient subsequently received 3 courses of chemotherapy with carboplatin and VP16, and 1 course of radiotherapy. However, the efficacy of the radiotherapy and chemotherapy was poor and the patient died due to metastatic disease on August 26, 2010.

Pathological analysis revealed the presence of SCCC that contained 15% adenoma. The mass of the tumor was 7 × 5 cm in size and infiltrated the cervical wall by more than 50%. Metastatic masses were observed on both sides of the cervical stroma. Most of the sentinel lymph nodes showed tumor thrombi. In addition, 75% of the left obturator lymph nodes and 50% of the right obturator lymph nodes contained metastatic cells.

Light microscopy showed normal squamous and aden epithelial cells on the surface of the cervix. The tumor was composed of small round cells, oval cells, and spindle cells (Image 2A). The tumor was diffusely distributed in the cervical stroma and a portion was nested. Importantly, the tumor cells infiltrated the cervical stroma, but not the surface lining (Image 2B). The cells were fairly uniform with hyperchromatic nuclei and a high nuclear-to-cytoplasmic ratio.
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Immunohistochemical staining showed that the cells were Syn (+) (Image 2C) and CK7 (+) (Image 2D). A fraction of the cells were also positive for CD117, but CgA (-), LCA (-), MyoD1 (-), Myogenin (-), Actin (-), and CD34 (-).

Discussion

SCCC is characterized as a poorly differentiated neuroendocrine group of cervical carcinomas. The American Association for Cancer Research categorizes neuroendocrine cervical carcinomas into the following 4 types: Typical, atypical, large cell, and small cell. Among them, the small cell type is more common and has a low survival rate. It is hypothesized that SCCC originates from reserve cells.

The diagnosis of SCCC is difficult, and therefore a pathologic examination is helpful. Pathological analysis combined with light microscopy, immunohistological staining, and electron microscopy can improve diagnosis. In this case, the biopsied sample exhibited a mass consisting of sheets of small, densely-packed cells that had hyperchromatic nuclei and a high nuclear-to-cytoplasmic ratio. For positive diagnosis, immunohistological staining of SCCC must show at least 1 positive epithelial and neuroendocrine marker, including CEA, CK, and CMA, as well as NSE, CgA, Syn, and CD56. However, to date there are no highly specific and sensitive markers for detection of SCCC.

The patient in this study was found to have 15% adenoma within the tumor as well as positive staining for Syn and CK7 in the tumor sample, which was used to diagnose SCCC. Recently, it was suggested that HPV is involved in the carcinogenesis of SCCC. The E6 protein of HPV can bind with p53 and inhibit protein function, which confers a p53 mutant phenotype. The HC2 test of this patient was 2507.06, which is a much higher value than that of a HPV negative patient. There are 13 high-risk HPV types, including 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. Retrospective data showed that the outcome of patients who were positive for CgA was worse than patients who were negative for CgA. In addition, the loss of p53 in patients also confers a poor prognosis.

SCCC is a rare malignancy with an incidence of 1%-3% of all carcinomas of the cervix; SCCC during late pregnancy is extremely rare. Reported cases of cervical cancer with pregnancy include cervical cancer diagnosed during the pregnancy, parturition, and postpartum stages. Sood et al suggested that cervical cancer diagnosed during the pregnancy, parturition, and postpartum stages is different than common cervical cancer. Cervical cancer occurs in 1/2000 to 1/10,000 of pregnant women and accounts for 0.5% of all cervical carcinomas. In addition, 80%-90% of these carcinomas are squamous cancers and the remaining types are adenomas. Similar to the presentation in patients who are not pregnant, SCCC during pregnancy presents with abnormal vaginal bleeding or vaginal discharge. The patient described in this study presented with abnormal...
vaginal bleeding for 1 month and was diagnosed with a threatening abortion at a community hospital.

In China, cervical liquid-based cytology is not commonly used in community hospitals and community doctors lack sufficient knowledge of cervical cancer. The patient never received a Papanicolaou (Pap) smear prior to the pregnancy, which contributed to the delay of treatment. Therefore, a patient with abnormal vaginal bleeding during pregnancy should be examined by cervical liquid-based cytology if abnormal bleeding cannot be attributed to pregnancy, including conditions such as threatened abortion, placenta previa, and placental abruption. Cervical liquid-based cytology can provide early detection of cervical malignancy; this procedure is recommended for women during pre-pregnancy and pregnancy stages for the early detection of pregnancy-related cervical carcinomas. However, the precise cytological interpretation of SCCC in conventional Pap smears is difficult due to low assay sensitivity and specificity, since SCCC often infiltrates into the cervical stroma and is not detectable at the surface. The liquid-based cytology Pap smears also have similar problems, but when used in combination with immunocytochemical and molecular analyses, can improve the diagnosis of SCCC.11

No optimal therapeutic approach has been identified for SCCC. Patients with early stage SCCC have better prognosis with surgery in combination with chemo-radiotherapy, but patients with later stages of SCCC should be given radiotherapy and concurrent chemotherapy. Hoskins et al reported that the therapeutic effects of SMCC1 (cisplatin and etoposide with involved-field irradiation) and SMCC2 (SMCC1 with carboplatin, paclitaxel, and para-aortic lymph node irradiation) were similar, but SMCC2 had fewer side effects.

The treatment of a pregnant SCCC patient is more complex than a patient with common cervical cancer. Patients with SCCC diagnosed during the early stages of pregnancy should have the pregnancy terminated and the patient should be treated with surgery combined with chemo-radiotherapy. At later stages of pregnancy, elective Cesarean section should be performed and subsequently combined with surgery and chemo-radiotherapy. The patient described here presented at 32-week gestation and wished to continue with her pregnancy. After the Cesarean section and radical hysterectomy, the patient was treated with 3 courses of chemotherapy and 1 course of radiotherapy. However, the efficacy of radiotherapy and chemotherapy was poor and the patient died due to metastasis.

The prognosis of SCCC patients is very poor and the survival time is very short. The time from diagnosis to recurrence typically is less than 35 months, and the mean duration from diagnosis to death is 14.19 months (ranging from 3-154 months). Several studies have reported a 5-year survival rate of 14%. Many factors can influence the prognosis, including the cancer stage, tumor size, extent of tumor infiltration, and vessel invasion. It is hypothesized that lymph node metastasis is the most important factor that influences prognosis. However, there is still a paucity of information in the literature regarding the efficacy of multimodal chemotherapy for SCCC. LM

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