Highly Aggressive Small-cell Neuroendocrine Carcinoma Cervix: A Rare Case Report

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ABSTRACT

Neuroendocrine tumors consist of a spectrum of malignancies that arise from the diffuse neuroendocrine cell system. Prognosis is dependent on histologic subtype and site of origin. The family of well-differentiated neoplasms (carcinoid and atypical carcinoid) is morphologically and clinically distinct from high-grade neuroendocrine carcinoma (small cell and large cell). This latter entity is closely related to pulmonary small-cell carcinoma, is highly aggressive and is generally managed with a multimodality approach including platinum-based chemotherapy. Neuroendocrine tumors primary to the gynecologic tract are still considered to be uncommon, with limited prospective data available to guide decision making. We are reporting a case of a highly aggressive small-cell neuroendocrine carcinoma cervix in a 38-year-old female with good initial response with chemotherapy and is under our follow-up.

Keywords: Neuroendocrine tumors, high-grade neuroendocrine carcinoma, platinum-based chemotherapy, small-cell neuroendocrine carcinoma cervix

CASE REPORT

Mrs. X, a 38-year-old lady, P3L3 attended Gyne OPD of ESI-PGIMSR, Basaidarapur, New Delhi on 13.5.2013 with the chief complaint of irregular bleeding per vaginum since 6 months. There was history of postcoital bleeding on and off since 6 months. Her past menstrual history was of regular periods. She was P3L3 with all full-term normal deliveries and her last childbirth was 15 years back. There was no history of any contraceptive usage. There was no history of tuberculosis (TB), thyroid disorder, diabetes mellitus (DM), hypertension (HTN). She was not addicted to smoking. Her vitals were stable. There was no lymphadenopathy.

Per speculum examination revealed a cauliflower growth, about 4 × 4 cm in sizes on the anterior lip of cervix. Four pea-sized growths were present on middle-third of vagina. On per vaginal examination, the findings of per speculum were confirmed, uterus appeared normal size with bilateral parametrium free. On per rectal examination, the rectal mucosa was free. Examination triggered active bleeding from the growth. The provisional diagnosis of cancer cervix ? cancer vagina was made. Patient was admitted and prepared for cervical biopsy and biopsy from the vaginal growth. Cervical smear for human papilloma virus (HPV) detection and typing along with the biopsy from cervical growth and vagina was taken. Patient was discharged with advice to follow-up with histopathology report. After 7 days, she reported with histopathology report showing ‘small-cell

Figure 1. M/E: Normal squamous epithelium, subepithelium shows tumor composed of small cells in sheaths (4X).

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neuroendocrine carcinoma of cervix and vagina’ (Fig. 1). The histopathologic diagnosis was facilitated with immunohistochemistry (IHC), which showed neuron specific enolase (NSE)-positive, chromogranin-positive, synaptophysin-positive, epithelial membrane antigen (EMA)-positive and carcinoembryonic antigen (CEA)-positive markers (Fig. 2). Since, these tumors originate from subepithelium, the marker of epithelial tissue cytokeratin-pan antibody monoclonal (CK-PAN) was negative. Cervical smear was negative for HPV infection.

She still had complaint of bleeding pervaginum on and off. There was no history of foul-smelling discharge. Her routine investigations including chest X-ray were within normal range. Review examination under anesthesia with vaginoscopy was planned.

It showed an irregular growth 4 × 4 cm present on anterior vaginal wall, 2 cm below the urethral meatus, extending up to the cervix. Cervix was replaced by fungating growth 6 cm in diameter.
Ultrasoundography (USG) upper abdomen was done and showed no abnormality. On per rectum, rectal mucosa was free. Clinical staging of Ca Cx Stage IIA 2 was made. Magnetic resonance imaging (MRI) abdomen and pelvis (30/5/2013) showed a heterogeneous mass lesion of 47 × 36 × 38 mm involving anterior wall of cervix and upper two-thirds of vagina (Fig. 4). The lesion was abutting posterior bladder wall, however, fat planes were maintained. Rest of uterus and ovaries were normal. There was no evidence of lymphadenopathy or free-fluid in the pelvis.

Positron emission tomography-computed tomography (PET-CT) scan (8/6/013) revealed metabolically active and bulky cervix and vagina, consistent with known primary. There were metabolically active small nodular opacities in both lung fields predominantly in subpleural regions in bilateral lungs suggestive of deposits. Metabolically active axillary, mediastinal and pelvic lymph nodes, bilateral obturator regions likely metastatic were present (Fig. 5). Metabolically active multiple skeletal lesions likely metastatic were identified. Imaging modalities staged the disease as an advanced case.

Patient was planned for chemotherapy with cisplatin and etoposide. Etoposide 100 mg/m² on Day 1, 2 and 3 and cisplatin 30 mg/m² on Day 1, 2 and 3 was given. After three cycles of chemotherapy, response assessment with PET-CT was done, which showed good treatment response and therefore, it was decided to give three more cycles with same chemotherapy. Presently, patient has received five cycles of chemotherapy and is under follow-up.

**DISCUSSION**

Most neuroendocrine cancers of the cervix are small-cell carcinomas, which account for up to 2% of cervical carcinomas.¹ They are characterized by high mitotic rate, extensive necrosis, frequent lymphovascular space involvement (LVSI) and a strong association with HPV-18.² Though, our case was negative for HPV infection, it was highly aggressive.

These highly aggressive tumors have a prognosis that is much worse than that for stage comparable with poorly differentiated squamous-cell carcinoma of the cervix. The median age of diagnosis is in the fifth decade (range 21-87 years). The usual presenting symptom is vaginal bleeding, and a cervical mass can often be identified on examination. Some patients have an abnormal Pap smear. The diagnosis is made on cervical biopsy. The staging of neuroendocrine carcinomas (NECs) of the cervix follows that for traditional cervical cancer. However, it is important to recognize the increased risk for lymphovascular space invasion and high rate of extrapelvic recurrences, which correlate with a poor prognosis. The mean time to recurrence was 19.9 months. Bone, supraclavicular lymph nodes and lung were the most common sites of extrapelvic disease spread. Radiographic evaluation should generally include either a CT or PET/CT scan.

Early stage disease are treated with multimodality regimens; recent reports have achieved an 80% 3-year disease-free survival. Radical hysterectomy with regional lymphadenectomy remains a component of the primary management. Patients with evidence of lymphadenopathy or fluorodeoxyglucose (FDG)-avid nodal basins may also be candidates for primary chemoradiation.³ Etoposide/cisplatin (EP) concurrent with pelvic radiation regimens are generally preferred over vincristine, actinomycin and cyclophosphamide (VAC)-containing regimens because they are less toxic.

Combination chemotherapy (EP) in addition to concurrent radiation can be used for advanced stage and recurrent disease. While initial response rates are high (50-79%), recurrent or progressive chemoresistant disease frequently develops.

The prognostic factors of the disease are advanced stage, tumor size, presence and number of lymph node metastases, pure small-cell histology.⁴,⁵ Smoking has been linked to a worse clinical outcome for small cell cervical cancer. Small-cell cervical cancers have a reported 5-year survival of 36%.

Clinical stage was the only independent predictor for disease-free survival, 80% at 3 years for Stage I/II and 38% for Stage III/IV.⁶ For surveillance frequent clinical evaluation including symptom review and pelvic examination is appropriate. Periodic full body imaging with either CT or PET/CT to evaluate for distant metastatic disease is appropriate. Brain imaging either with head CT or MRI should be considered in presence of neurologic symptoms or pulmonary metastasis.

Newer chemotherapy treatments such as temozolomide and multiple molecular targets for treatment of NECs have been identified.Potential therapeutic targets include CD56, a neural cell adhesion molecule that is expressed by neuroendocrine cancers. A monoclonal antibody for CD56, linked to the cytotoxic compound DM-1 is in phase II trials. Src kinase, a tyrosine kinase, which has differential expression in both small cell and nonsmall-cell lung cancer, is another potential target.
The Hedgehog pathway and Bcl-2 represent other areas of investigation.

CONCLUSION

To conclude, small-cell neuroendocrine tumor cervix is a rare tumor, accounting for up to 2% of all cervical carcinomas. It is closely related to pulmonary small-cell carcinoma, is highly aggressive and is generally managed with a multimodality approach. It has poor prognosis. Treatment for advanced stage is with chemoradiation.

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REFERENCES


Women Above 65 to Take Extra Care of their Health

- Women aged 65 and above should take low-dose aspirin routinely to prevent heart attack and paralysis.
- All women are urged to exercise a minimum of 30 minutes/day, but women who need to lose weight or maintain weight loss are now advised to engage in 60-90 minutes of moderate-intensity activity on most, or preferably all, days of the week.
- A heart-healthy diet should be rich in fruits, whole grains and fiber foods with a limited intake of alcohol and sodium.
- Saturated fat should be reduced to less than 7% of calories.
- Women at very high-risk for heart disease should try to lower their LDL (‘bad’) cholesterol to <70 mg/dL.
- Women aged 65 and over should consider taking low-dose aspirin on a routine basis, regardless of their risk.
- Aspirin has been shown to prevent both heart attacks and stroke in this age group.
- The upper dose of aspirin for high-risk women is 325 mg/day.
- Hormone replacement therapy, selective estrogen receptor modulators nor antioxidant supplements such as vitamins C and E should be used to prevent heart disease.
- Folic acid should also not be used to prevent cardiovascular disease.
- Women should eat oily fish or some other source of omega-3 fatty acids at least twice a week.
- Women should not only quit smoking but should use counseling, nicotine replacement or other forms of smoking cessation therapy.
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