Case Report

Small-cell neuroendocrine carcinoma cervix: A case report of an aggressive tumor

R. K. Spartacus, Rohitashwa Dana, Nirupama Kothari[1], Rajan Paliwal[2]

Department of Radiotherapy, SMS Medical College and Attached Hospitals, [1]Super Religare Laboratories Diagnostic, [2]Department of Radiotherapy, Dr. S.N. Medical College, Jaipur, Rajasthan, India

ABSTRACT

Neuroendocrine tumors comprise a broad family of tumors that arise from the diffuse neuroendocrine cell system. Small-cell neuroendocrine carcinoma cervix is a rare tumor, accounting for up to 2% of cervical carcinomas. These are highly aggressive tumors, characterized by early distant metastasis and worse prognosis compared to other histological types occurring in the cervix. Distant sites of recurrence including lung and bone are more common (28%) than local failure (13%). We report a case of a 60-year-old woman whose disease progressed during treatment with an eventual fatal outcome.

Key words: Aggressive, cervix, rare, small-cell neuroendocrine carcinoma

INTRODUCTION

Neuroendocrine tumors comprise a broad family of tumors that arise from the diffuse neuroendocrine cell system. They usually arise in the lungs and bronchi, small intestine, appendix, rectum, pancreas, and thymus. The uterine cervix is a very unusual site. Most neuroendocrine cancers (NECs) of the cervix are small-cell carcinomas, accounting for up to 2% of cervical carcinomas.[1] These tumors are characterized by an earlier distant metastasis and a worse prognosis compared with other histological types occurring in the cervix.[2] Small-cell cervical cancers have a reported 5-year survival of 36%.[1]

CASE REPORT

A 60-year-old woman of rural background presented with lower abdominal pain and per vaginal bleeding. Pelvic examination revealed a large ulceroproliferative growth replacing cervix, involving all fornices and the upper half of the vaginal wall. Rectal mucosa was mobile, and parametria were uninvolved. Magnetic resonance imaging of the pelvis and abdomen supported the clinical findings, revealing a poorly marginated circumferential expansile mass of uterine cervix of 3.1 cm × 5.1 cm × 3.6 cm isointense on T1-weighted (T1W) and hyperintense on T2W, with infiltration into endocervical canal. Her chest X-ray was normal. Clinically, there was no evidence of any lymphadenopathy. Positron emission tomography-computed tomography could not be done because of financial constraints. Biopsy of the mass showed tumor comprising small round cells arranged in large groups separated by connective tissue stroma. The cells had scanty cytoplasm and round nucleus with dense chromatin without nucleoli [Figure 1]. Immunohistochemistry (IHC) was carried out and tested positive for pan cytokeratin [Figure 2a], synaptophysin [Figure 2b], and chromogranin A [Figure 2c], suggestive of neuroendocrine carcinoma.

The patient was started on a regimen of cisplatin (25 mg/m^2) and etoposide (100 mg/m^2), both given on days 1, 2, and 3, with an intention of radical hysterectomy and

Address for correspondence: Dr. R. K. Spartacus, Department of Radiotherapy, SMS Medical College and Attached Hospitals, Jaipur, Rajasthan, India.
E-mail: meg80224@gmail.com

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lymphadenectomy after the neoadjuvant chemotherapy. After three cycles of chemotherapy, response evaluation was done. The cervical mass showed regression. However, she developed multiple para-aortic metastases [Figure 3] and bilateral inguinal lymphadenopathy. The disease status and prognosis was explained. She did not turn up for further treatment for the next 2 months. A phone call to her husband confirmed her demise.

DISCUSSION

Small-cell neuroendocrine cervical cancer (SCNCC) is a rare and aggressive tumor. In 1997, a workshop sponsored by the College of American Pathologists and the National Cancer Institute proposed a standardized terminology for neuroendocrine tumors of the uterine cervix. The nomenclature was created as a parallel to that used for pulmonary endocrine tumors. Four categories were identified small-cell carcinoma, large cell neuroendocrine carcinomas, typical carcinoid tumors, and atypical carcinoid tumors.[3]

SCNCC exhibits clinical and biological characteristics of both cervical neoplasm (such as local aggressiveness and involvement of papillomavirus) and neuroendocrine small-cell cancer of any site (such as early dissemination of the disease and loss of heterozygosity at different loci). They are characterized by high mitotic rate, extensive necrosis, frequent lymphovascular space involvement (LVSI), and a strong association with human papillomavirus-18. It is important to differentiate this entity (by immunohistochemical analysis) from other small blue cell tumors that can arise in the cervix and mimic small-cell carcinoma such as basaloid squamous cell carcinoma, embryonal rhabdomyosarcoma, lymphoma, and undifferentiated carcinoma.[4] Immunohistochemical studies such as synaptophysin, CD56, and chromogranin A detect neuroendocrine differentiation, and strong Ki-67/MIB-1 labeling indicates the malignant characteristics of neuroendocrine tumors.[2] Our case tested positive for pan cytokeratin, synaptophysin, and chromogranin, suggestive of neuroendocrine carcinoma.

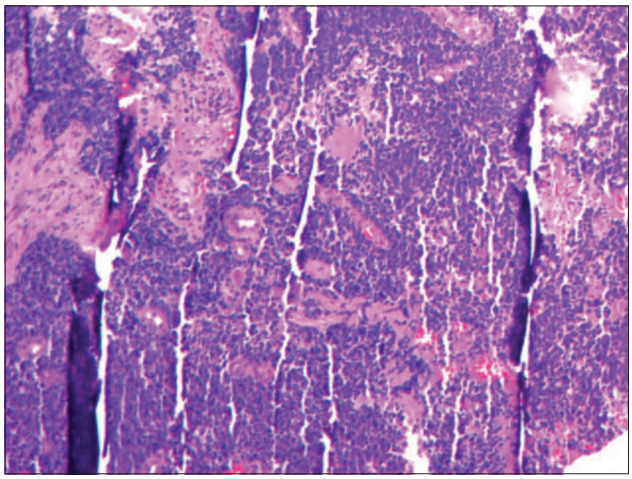

Figure 1: Tumor comprising small round cells arranged in large groups separated by connective tissue stroma. The cells have scanty cytoplasm and round nucleus with dense chromatin without nucleoli

The median age of diagnosis is in the fifth decade (range: 21–87 years). The usual presenting symptoms are vaginal bleeding and a cervical mass on examination. The staging of NECs of the cervix follows that for traditional cervical cancer; however, they do not follow the locoregional pattern of the spread of cervical cancer. Even in stage IB1 tumors, there is 40% of pelvic lymph node involvement and 60% of LVSI, and these correlate with their aggressiveness and poor prognosis. There is a high rate of extrapelvic recurrences. Bone, supraclavicular lymph nodes, and lung are the most common sites of extrapelvic disease spread. Distant sites of recurrence including lung and bone are more common (28%) than local failure (13%).[1] Prognostic factors identified for this entity include the stage at presentation, tumor size, presence and number of lymph node metastases, pure small-cell histology, and smoking history.[5,6]

Treatment considerations for small-cell NEC of the cervix take into account the treatment options for cervical cancer and draw on the data for treating small-cell lung cancer. In 2003, Chan *et al*. proposed a management algorithm for small-cell carcinoma of the cervix.[5] The Society of Gynecologic Oncology (SGO) in view of their detailed review in 2011 modified the approach and proposed that for early stage (International Federation of Gynecology and Obstetrics I–IIA) tumors <4 cm, radical hysterectomy with lymphadenectomy can be performed with the consideration of etoposide/platinum (EP)-based therapies in the adjuvant setting. Tumors larger than 4 cm could be considered for a neoadjuvant approach with systemic

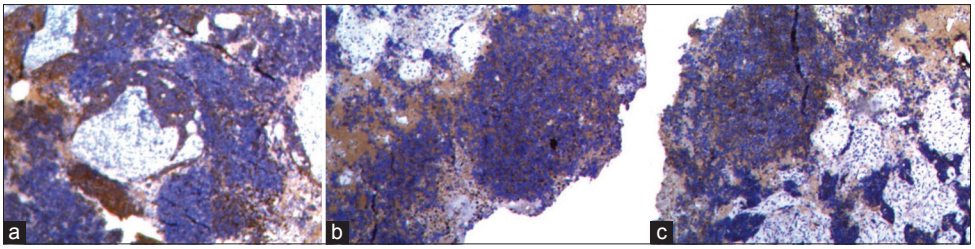

Figure 2: Immunohistochemistry showing positive staining for pan cytokeratin (a), synaptophysin (b), and chromogranin A (c)

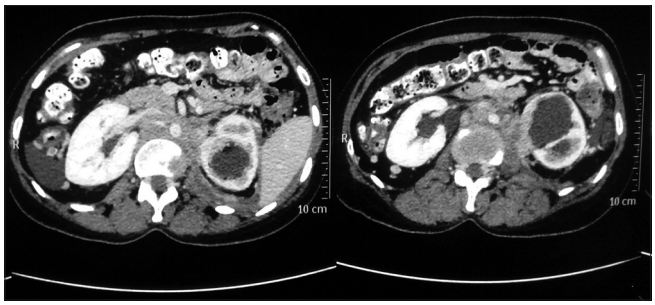

Figure 3: Computed tomography scan showing multiple para-aortic lymph node metastases

platinum-based therapies followed by a localized treatment-based approach (including surgery) if the disease remains limited. In late stage or nonsurgical candidates, combination chemotherapy (EP) with radiotherapy for local control should be considered.[1] In summary, the SGO group recommended a multimodality therapeutic approach keeping individualized treatment considerations.

CONCLUSION

SCNCC is a rare and highly aggressive tumor. It is important to recognize this separate histopathological entity (IHC analysis), followed by a detailed systemic assessment considering the high rate of distant metastatic spread and a multimodality therapeutic approach to maximize the treatment.

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Conflicts of interest

There are no conflicts of interest.

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