Case Report

Small Cell Neuroendocrine Carcinoma of Cervix: A Rare Case Report

Kavita Jain[1], *P K Roy*[2]

Neuroendocrine neoplasms (NEN) are derived from endocrine cells and are very rarely seen in gynecological practice. Here we report a case of small cell neuroendocrine carcinoma (SCNEC) of cervix in a 45 year old married female who presented with history of menorrhagia. On gynecological examination, she had bulky uterus with a palpable non-tender, hard nodule on the posterior wall of the cervix. An ultrasonogram of the pelvis was reported as bulky? Adenomyotic uterus with 2.7 x 2.4 x 1.0 cm well-defined collection in the fundal region of the endometrium. She underwent total abdominal hysterectomy for abnormal uterine bleeding. Histopathology with immunohistochemical markers was reported as SCNEC of cervix. This case is reported here for its rarity.

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Introduction

Neuroendocrine neoplasms (NEN) in female genital tract are rare and are either differentiated neuroendocrine tumors (NET) or poorly differentiated neuroendocrine carcinoma (NEC). Of these, NET's are commonly seen in ovary, are benign by nature and morphologically correspond to carcinoid tumors, arising from a dermoid cyst.[1] On the other hand, NEC are seen in cervix though they account for only 0.9- 1.5% of all cervix cancers.[2] By definition, they are high grade and are of two morphological types, small cell (SCNEC) and large cell NEC.[1] Most of the cases of SCNEC are associated with high risk HPV infection.[3] These patients present with symptoms such as vaginal bleeding, post-coital spotting, lower abdominal pain with cervical growth, that may or may not be ulcerated. These symptoms and clinical findings do not help to differentiate them from other more common types of cervical malignancies like squamous cell carcinoma or adenocarcinoma. Diagnosis is primarily made on histopathology with the help of immunohistochemistry in order to differntiate them from poorly differentiated squamous cell carcinoma or adenocarcinoma.

Case Report

45 year old married female presented with nearly two months history of menorrhagia to department of obstetrics and gynecology. On examination, she had bulky uterus with a hypertrophied cervix. A palpable non-tender, hard nodule was present on posterior wall of cervix that bled on touch. She was a multipara with three live borns by normal vaginal delivery and had undergone bilateral tubectomy about 15 years back. There was no history of any other illness such has hypertension, diabetes, thyroid disorder or asthma. She had never undergone blood transfusion or parenteral iron therapy. At admission, her routine haemotological workup showed microcytic hypochromic anaemia with haemoglobin of 8.9 gm/dl and mild reactive thrombocytosis. Her white blood cell count was within normal limits. Routine biochemical and serological workup were also normal. An ultrasonogram of pelvis was reported as bulky ? adenomyotic uterus with 2.7 x 2.4 x 1.0 cm well defined collection in fundal

[1]Department of Pathology, R.D Gardi Medical College, Ujjain, Madhya Pradesh, India.

[2]Department of Obstetrics and Gynaecology, R.D Gardi Medical College, Ujjain, Madhya Pradesh, India.

Correspondence to: Kavita Jain, Department of Pathology, R.D Gardi Medical College, Ujjain, Madhya Pradesh, India. E-mail: kjain1974@rediffmail.com

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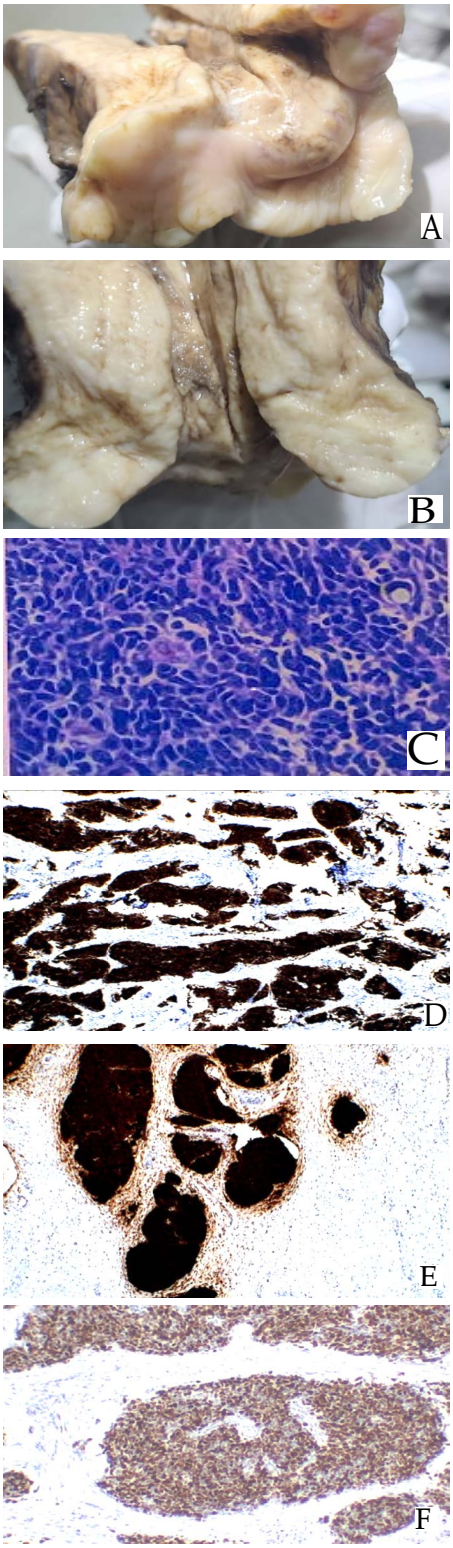

Figure 1: a,b- gross photos of specimen with polypoid growth in cervix and depressed hard puckered area in rest of the cervix respectively; c- photomicrograph showing tumor cells with hyperchromatic nuclei, H and E stained- x400; d,e,f: photomicrographs showing tumour cells are immunopositive for synaptophysin and CD56 with ki67 proliferation index of 90% respectively.

region of endometrium. Her endometrial biopsy was sent for histopathology and on the next day she underwent total abdominal hysterectomy with clinical diagnosis of abnormal uterine bleeding.

Histopathology: Initially, we received endometrial biopsy tissue as multiple brownish tissue bits, aggregate measuring 1.5 x 1.0 x 0.5 cm. Entire tissue was processed. On microscopy, the section showed endometrial fragments with normal gland to stroma ratio along with stromal invasion by nests and clusters of cells with enlarged hyperchromatic nuclei, scant cytoplasm, nuclear molding and brisk mitotic activity. Focal rosetting was also seen. A diagnosis of poorly differentiated malignant tumor was given. Serum CEA and chromogranin levels were suggested along with immunohistochemistry (CK8/18, CK5/6, p40/p63, chromogranin, synaptophysin, CD56, p16, desmin, SMA, LCA) for further evaluation of tumor type. The patient underwent total abdominal hysterectomy on the next day of endometrial curettage with clinical diagnosis of abnormal uterine bleeding. Grossly, uterus with cervix weighed 350 gm and measured 15 x 8 x 4 cm. On cut open, cervix measured 4.5 cm in length. Its posterior wall showed a firm lobulated polypoid growth measuring 2 x 1.5 x 1.0 cm with creamish white firm to hard surface (Figure 1a). Rest of the cervix was hard and had irregular depressed puckered surface (Figure 1b). Enodmetrium measured 1.5 cm in maximum thickness. Myometrium measured 3.2 cm in thickness and was studded with tiny nodules, involving more than half of its maximum thickness. Attached part of vaginal cuff measured 1.5 cm in width. No attached parametrial tissue was seen, however, a second container contained specimen labeled as unknown tissue which was greyish brown, firm and measured 1.3 x 1.0 x 0.5 cm.

On microscopy, sections from cervix showed normal ectocervical epithelium and cervical glands with no dysplasia. Sections from the polypoid growth in posterior wall of cervix and rest of the cervical stroma showed infiltrating nests and clusters of neoplastic cells as seen in endometrial biopsy. These cells were predominantly small with scant cytoplasm and had enlarged hyperchromatic nuclei (Figure 1c). Nuclear molding and 14 mitotic high power fields were present. Lymphatic tumor emboli were seen with areas of necrosis but there was no tumor infiltration by lymphocytes. Sections from lower and upper uterine segment showed invasion of more than 50% of myometrial thickness and focal endometrial stromal invasion by similar neoplastic cells. There was no evidence of endometrial hyperplasia. Sections from

vaginal cuff were free of tumors. A specimen in second container showed blood vessels and neoplastic cell clusters in fibrocollagenous tissue (parametrial tissue).

Diagnosis on light microscopy remained as poorly differentiated malignant tumor of cervix with lymphatic tumour emboli and spread to parametrial tissue (unknown tissue). Immunohistochemical markers showed that tumor cells were immunopositive for synaptophysin, CD56 with ki 67 proliferation index of 90% (Figure 1 (d-f)), respectively. The tumor cells were also immunopositive for CK, p16 and PAX8. A final diagnosis of Small cell neuroendocrine carcinoma of cervix was made (FIGO stage IIB).

Discussion

As per Globocan 2020, new cases of carcinoma cervix accounts for 3.1% of all cancers. In India, it is the 3rd most common cancer with incidence rate of 18.3% and second leading cause of death due to cancer with a mortality rate of 9.1%.[4] Squamous cell carcinoma and adenocarcinoma are the common types of cancer seen in cervix. Most of these cases (99%) are associated with high risk types of Human papillomavirus (HPV). Gynecological neuroendocrine neoplasms (NEN) are very rare and accounts for only 1.2-2.4% of all NEN and 0.9-1.5% of cervical cancers.[5,2] Of these gynecological NEN, small cell neuroendocrine carcinomas are most commonly seen in cervix.[1]Their diagnosis is made on histopathology with supporting immunohistochemical markers as clinically they cannot be distinguished from the more common squamous cell carcinoma and adenocarcinoma of cervix. These tumors have very poor prognoses and are difficult to treat due to lack of standardized treatment guidelines for gynecological NEN based on clinical trials and are thus considered a therapeutic challenge by oncologists.[6] They arise from argyrophilic cells in ectocervix and endocervix and have an increased propensity for lymphatic and hematogenous spread.[7] They are often associated with nodal metastasis even when they clinically seem to be limited to cervix.

The mean age of occurrence of these tumors is in the forties as in our case. They usually have the same clinical symptoms and findings as seen in squamous cell carcinoma or adenocarcinoma of cervix. Menorrhagia, vaginal spotting and lower abdominal pain are the usual symptoms. Clinically they present as growth in cervix which may or may not be ulcerated. Katajima et al described the MRI findings in 62 cases of cervical NEC studied retrospectively. A homogenous textured lesion with obvious restricted diffusion throughout the tumor are findings which help in diagnosing the probability of cervical NEC on MRI pelvis. Also MRI will reliably help to 'T'stage these cancers and is thus recommended in all suspected cervix malignancies.[8]

Histomorphological, they have the same appearance as small cell carcinoma of lungs and elsewhere. Neoplastic small cells are seen in solid sheets, nests and clusters with sometimes pseudo rosette formation. These cells have scant cytoplasm with enlarged hyperchromatic nuclei and show nuclear molding with very brisk mitotic activity, necrosis and crush artifact. Absence of inflammatory cell infiltrate has been noted in addition to above features. Their differential diagnosis on histopathology are poorly differentiated squamous cell carcinoma with small cells, poorly differentiated adenocarcinoma, small round cell tumours like rhabdomyosarcoma, lymphoma, primitive neuroectodermal tumours and others like melanoma and endometrial sarcoma. Also, though they are usually seen in pure form, synchronous invasive or in-situ squamous cell carcinoma or adenocarcinoma has also been noted in a few cases. Castle et al in their study showed that 85% of SCNEC were associated with human papillomavirus (HPV) and that they can be prevented by use of prophylactic HPV vaccine.[9]

Immunohistochemical markers like chromogranin A, synaptophysin and CD56 help to confirm the diagnosis. Chromogranin A is a more specific marker and synaptophysin, CD56 are more sensitive markers of neuroendocrine differentiation. Ki67 proliferation index in all these tumors is very high and ranges from 45 to 98% (median of 87.5%). PAX 8 immunopositive profile is seen in tumors of mullerian origin while p16 expression suggests cervical origin as neither CDX2 nor TTF1 will help to distinguish from cervical metastasis of NEC from intestinal tract or lungs. Immuno negativity for p40 will help to distinguish from squamous cell carcinoma of cervix.[5] Other markers such as desmin, LCA will help to rule out rabdomyosarcoma or lymphoma.

Prognosis is poor for gynecological SCNEC and depends on FIGO stage, age of patient, tumor size and nodal metastasis. Multimodality treatment is followed in the form of radical hysterectomy with adjuvant chemotherapy/ chemoradiation or neoadjuvant chemotherapy followed by radical hysterectomy for early stage cancer. In locally advanced disease, concurrent chemoradiation and palliative chemotherapy for metastatic disease is given. Chemotherapy regimen is similar to what is followed for neuroendocrine tumors of lung. First line chemotherapy regimen for neuroendocrinr

tumors is combination of cisplatin and etoposide. New alternate strategies have been offered by Salvo et al and reviewed by other authors. Novel therapeutics such as immune checkpoint inhibitors and targeted therapies should be used and evaluated for better outcome as till now despite multimodal treatment, five year survival rate is documented as 36% with a median overall survival of 22-25 months.[2, 3,6,7,10]

In our case, the patient was a 45 year old with history of menorrhagia and cervical growth. On histopathology aided with immunohistochemistry, she was diagnosed with small cell carcinoma of cervix, FIGO stage IIB.

Conclusions

Gynecological NEN and especially SCNEC are extremely rare malignancies. Due to the poor prognosis associated with gynecological SNEC, it is very important to diagnose these rare gynecological malignancies at the earliest. Upfront use of best treatment regimen, tailored to the individual case, involving a team of gynecologists, medical oncologists and radiation oncologists might help improve their outcome. This case report is intended to familiarize all practicing pathologists and treating gynecologists about this rare and difficult to treat gynecological malignancy.

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References

1. Rindi, G., Klimstra, D.S., Abedi-Ardekani, B. et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol 31, 1770–1786 (2018). https://doi.org/10.1038/s41379-018-0110-y
2. Aletti G, Laffi A. Neuroendocrine tumors of the cervix: an urgent call for joining forces International Journal of Gynecologic Cancer 2019;29:985.
3. Lu J, Li Y and Wang J (2022) Small Cell (Neuroendocrine) Carcinoma of the Cervix: An Analysis for 19 Cases and Literature Review. Front. Cell. Infect. Microbiol. 12:916506. doi: 10.3389/fcimb.2022.916506
4. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.fr/today, accessed [10.11.2022]
5. Inzani F, Santoro A, Angelico G, Feraco A, Spadola S, Arciuolo D, Valente M, Carlino A, Piermattei A, Scaglione G, Scambia G, Rindi G, Zannoni GF. Neuroendocrine Carcinoma of the Uterine Cervix: A Clinicopathologic and Immunohistochemical Study with Focus on Novel Markers (Sst2–Sst5). *Cancers*. 2020; 12(5):1211. https://doi.org/10.3390/cancers12051211
6. Tempfer CB, Tischoff I, Dogan A, Hilal Z, Schultheis B, Kern P, Rezniczek GA. Neuroendocrine carcinoma of the cervix: a systematic review of the literature. BMC Cancer. 2018 May 4;18(1):530. doi: 10.1186/s12885-018-4447-x. PMID: 29728073; PMCID: PMC5935948.
7. Kumar T, Nigam J S, Kumari M, et al. (June 08, 2021) Cervical Neuroendocrine Carcinoma: A Rare Case Report. Cureus 13(6): e15532. doi:10.7759/cureus.15532
8. Kitajima K., Kihara T., Kawanaka Y., Kido A., Yoshida K., Mizumoto Y., Tomiyama A., Okuda S., Jinzaki M., Kato F., Takahama J., Takahata A., Fukukura Y., et al Neuroendocrine carcinoma of uterine cervix findings shown by MRI for staging and survival analysis – Japan multicenter study. Oncotarget. 2020; 11: 3675-3686.
9. Castle PE, Pierz A, Stoler MH: A systematic review and meta-analysis on the attribution of human papillomavirus (HPV) in neuroendocrine cancers of the cervix. Gynecol Oncol. 2018, 148:422-9. 10.1016/j.ygyno.2017.12.001
10. Salvo G, Gonzalez Martin A, Gonzales NR, Frumovitz M: Updates and management algorithm for neuroendocrine tumors of the uterine cervix. Int J Gynecol Cancer. 2019, 29:986-95. 10.1136/ijgc-2019- 000504