LARGE CELL NEUROENDOCRINE CARCINOMA OF UTERINE CERVIX-A CASE REPORT

SHANTHA MEENA

Department of Obstetrics and Gynaecology, COIMBATORE MEDICAL COLLEGE

Abstract: Large cell neuroendocrine carcinoma of the uterine cervix is a rare malignancy accounting for less than 5 of all cervical malignancies(1). It is a highly aggressive tumour with poor prognosis. It has a high propensity to metastasize even at its early stage despite multimodality treatment strategy. A case report of a 60 year old woman presented at the Gynaecology OPD in Coimbatore Medical College Hospital with complaints of postmenopausal bleeding having a cauliflower like cervical growth histopathologically showing neuroendocrine differentiation of large cell type has been described.

Keyword: Large cell neuroendocrine carcinoma, uterine cervix

INTRODUCTION:

Neuroendocrine tumours of the uterine cervix are a group of rare malignancies characterised by highly aggressive behaviour and are prone to early metastasis. They are classified as:

a) Typical carcinoid
b) Atypical carcinoid
c) Small cell carcinoma
d) Large cell neuroendocrine carcinoma based on mitotic activity, nuclear atypia and geographic type of necrosis (2).

In contrast to small cell carcinoma whose aggressive behaviour and resistance to therapy has been well established, cervical large cell neuroendocrine carcinoma was often under-recognised and misdiagnosed as poorly differentiated adenocarcinoma or squamous cell carcinoma (3).

Prognosis remains poor for these patients despite multimodality treatment and the majority of patients die within 2 to 3 years of diagnosis. The five year survival rate is around 14-39% similar to that of the small cell carcinoma (4).

CASE REPORT:

60 years old women belonging to socioeconomic class 4 presented with complaints of postmenopausal bleeding and loss of appetite for one month duration. Bleeding was scanty occurring on and off. She attained menopause 15 years back. Her parity index was para 9, living 9 (P9L9) all fullterm normal vaginal deliveries. There was no significant past medical and surgical illness. There was no family history of gynaecological malignancy, breast cancer. On examination patient was moderately built, illnourished, anaemic, no pedal edema, no lymphadenopathy, breast and thyroid normal.

Vitals stable.

Per abdomen: soft, not tender, no organomegaly, no free fluid, sterilisation scar healthy. Per speculum examination - cervix replaced by a cauliflower like ulceroproliferative growth. Bimanual examination - cervix replaced by the same ulceroproliferative growth of about 5x4 cm size involving both the lips, it was friable, bleeds on touch. Upper third of vaginal wall involved. Uterus anteverted and normal in size. All fornices indurated.

Per rectal examination - both parametrium involved not extending to pelvic side wall. Rectal mucosa free. Clinically diagnosed as carcinoma cervix and cervix biopsy was taken proceeded with further investigations.

Investigations:

- Hemoglobin - 6.1 g/. Blood sugar - 84 mg,
- Urea - 32 mg, serum creatinine - 0.1 mg/l, liver function tests appear normal.
- Chest x-ray showed multiple well defined radiopacities in right paracardiac region near hilum – Nodal metastasis. ECG appears normal.
- Ultrasound - uterus bulky, large hypoechoic mass seen in the region of cervix, both ovaries not visualised, other organs normal, no free fluid.

Cervix biopsy HPE: Malignant tumour composed of monotonous population of medium to large sized round cells arranged in diffuse pattern, cytoplasm is amphophilic. Nucleus is vesicular, large, round with prominent nucleoli. Nuclear membrane is irregular. Mitotic figures 8 to 10 seen. Areas of geographic necrosis seen. Impression: Neuroendocrine Carcinoma - Large Cell type (FIG 1, FIG 2)

Immunohistochemistry (FIG 3):

- Cytokeratin-negative
- Neuron specific Enolase – Strongly positive
- Chromogranin A – Focally positive
- Synaptophysin-negative

fig 1 - HPE CANCER CERVIX LARGE CELL CARCINOMA
and Neuron Specific Enolase and absence of Cytokeratin. Neuroendocrine markers such as Chromogranin A, Synaptophysin. Neuroendocrine differentiation is demonstrated with pan minimal cytoplasm, abundant mitosis, extensive necrosis - No cytological atypia, rare mitosis, no nucleosis.

**Diagnosis - CARCINOMA CERVIX STAGE 4B (lung metastasis) -NEUROENDOCRINE TUMOUR OF LARGE CELL TYPE.**

Patient was transfused with three units of packed cells and haemoglobin improved to 10 grams. Oncology opinion was obtained, suggested to start on palliative chemotherapy. Patient was started on combination palliative chemotherapy - Cisplatin and Etoposide. Patient tolerated first cycle of chemotherapy well. She was advised to come for the second cycle of chemotherapy after 21 days.

**DISCUSSION:**

Knowledge on large cell neuroendocrine carcinoma of the uterine cervix has gradually accumulated over the past two decades since a clear classification of cervical neuroendocrine tumours was established in 1997. In 1997, a workshop was convened under auspices of the College of American Pathologists and the National Cancer Institute to clarify the issues of classifying Neuroendocrine Cancers. A new classification was proposed that encompasses for entities (2). Typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma, small cell carcinoma.

This classification scheme is identical to that used for pulmonary neuroendocrine neoplasms and uses the same diagnostic criteria for each of the entities. **Etiology:** Integration of high risk Human Papilloma Virus (HPV) particularly HPV 16 and to a lesser extent HPV-18 is associated with large cell neuroendocrine carcinoma (5). **Clinical presentation:** Early stage cases presents with irregular vaginal bleeding, postcoital spotting, serosanguineous vaginal discharge (6). Pelvic examination may reveal either cervical erosion or a cervical growth. Clinical carcinoid syndrome in the neuroendocrine tumour of cervix is very unusual. Frequent metastatic sites include central nervous system, lung and bone. Histopathological Criteria for the diagnosis of NEC of uterine cervix

**Classical carcinoid** - No cytological atypia, rare mitosis, no necrosis. **Atypical carcinoid** - Cytological atypia seen, 10 mitotic figures, focal necrosis. **Large cell type** - Large cells with large vesicular nuclei and prominent nucleoli, > 10 mitotic figures, geographic necrosis. **Small cell carcinoma** - Small round cells with minimal cytoplasm, abundant mitosis, extensive necrosis. Neuroendocrine differentiation is demonstrated with pan neuroendocrine markers such as Chromogranin A, Synaptophysin and Neuron Specific Enolase and absence of Cytokeratin.

It is quite possible that large cell neuroendocrine cancers are frequently misdiagnosed as poorly differentiated squamous cell carcinomas or adenocarcinomas based upon the identification of focal areas of squamous or glandular differentiation respectively (3). In such cases, the subtle neuroendocrine features of large cell carcinoma are easily overlooked, but neuroendocrine markers would help.

Due to rarity of cervical large cell neuroendocrine cancers, no consenses has been reached on an optimal treatment plan and current multimodality treatment strategies that combine radical hysterectomy with or without bilateral salpingo-oophorectomy, chemotherapy and radiotherapy are mainly adapted from treatments used for neuroendocrine carcinomas of the lung (7).

For early stage cancer cervix 1A - II A of size less than 4 cm the optimal treatment plan was Radical hysterectomy and lymphadenectomy followed by chemotherapy with or without Radiotherapy, if the tumour size was more than 4 cm Neoadjuvant Chemotherapy followed by surgery or Chemoradiation was suggested. For late stage carcinoma cervix III B - IV B the optimal management was combination chemotherapy and chemoradiation. Cisplatin and Etoposide combination chemotherapy is most commonly used. Other regimens include Vinoreline, Doxorubicin, Cyclophosphamide (VAC), Carboplatin plus Paclitaxel, occasionally Epirubicin, Topotecan is used. **Surveillance:** Frequent clinical evaluation including symptom review and pelvic examination is appropriate. Periodic full body imaging with either CT or PET scan to evaluate distant metastatic sites including lung, brain, bone is appropriate.

Brain imaging either with head CT or MRI should be considered if neurological symptoms, mental status changes or pulmonary metastasis are identified. (8) However regardless of great efforts invested the majority of large cell neuroendocrine cancer patients do not survive more than two years after being diagnosed. Nodal treatment strategies have been developed that require further evaluation include hormonal treatment and somatostatin analogue, Octreotide.

**CONCLUSION:** Recognition of this rare and aggressive tumour is important for planning effective treatment but the optimal mode of therapy remains controversial. As it is a highly aggressive tumour with poor prognosis, multimodality treatment is advised in an attempt to reduce mortality. Yet the poor prognosis indicates that more reports and studies are needed to formulate the most appropriate therapy for the patients with large cell neuroendocrine tumour of uterine cervix.

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