

Large Cell Neuroendocrine Cancer (LCNEC) of uterine cervix: A case study and review of literature

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Citation

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Abstract

Large cell neuroendocrine carcinoma (LCNEC) of the uterine cervix is a very rare malignancy (less than 5% of all cervical malignancies) that is highly aggressive and usually results in unfavorable outcomes^{1,2}. These tumors have been classified into four categories: small cell, large cell, classic carcinoid, and atypical carcinoid. Most patients with early stage disease develop metastatic disease. Frequent metastatic sites include the central nervous system, lung, and bone³. Despite aggressive surgical therapy, even in early-stage patients, mortality is high. This propensity for rapid, local and distant spread in early-stage disease emphasizes the need for systemic treatment². In some cases, the initial diagnosis may be confused with either poorly differentiated squamous- or adeno-carcinomas³.

CASE HISTORY

A 45 year old, multipare, whose last childbirth was 5 years ago, presented with a history of irregular bleeding and whitish discharge per vagina for the last 6 to 7 months. She had no other complaints. On pelvic examination, there was a growth of 4 x 4 cm, arising from the posterior lip of the cervix. The growth was soft and bled on touch. Uterine size was normal, no parametrial thickening, and no adnexal masses could be palpated. She was advised to have a diagnostic biopsy which she declined and did not come back for follow up for the next five months. Because she still refused a biopsy, a total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. Part of the parametrium was also excised along with the uterus which looked grossly normal. There was no ascites, no abnormality in the abdominal viscera and no palpable lymph nodes. Uterine body, tubes and ovaries looked normal. The post operative period was uneventful.

RESULTS

Grossly, on cut section, the tumor showed a yellowish white mass located in the posterior lip of cervix, measuring approximately 4 cm in diameter with gray-white areas (Fig. 1).

Figure 1

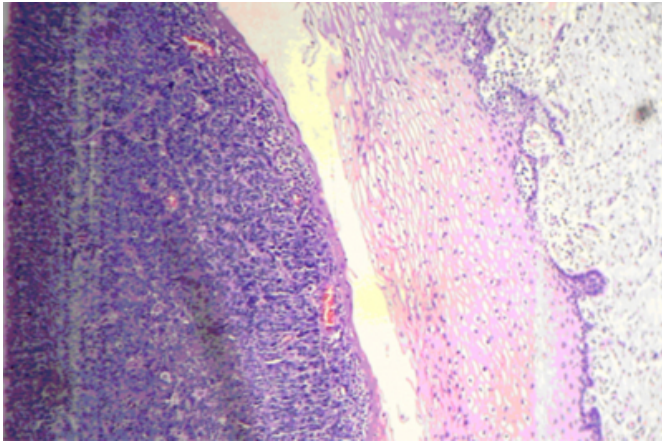
Figure 1: Gross specimen



Tissues were sectioned, stained with hematoxylin and eosin and evaluated under light microscopy. The sections showed tissue lined by stratified squamous epithelium (Fig. 2).

Figure 2

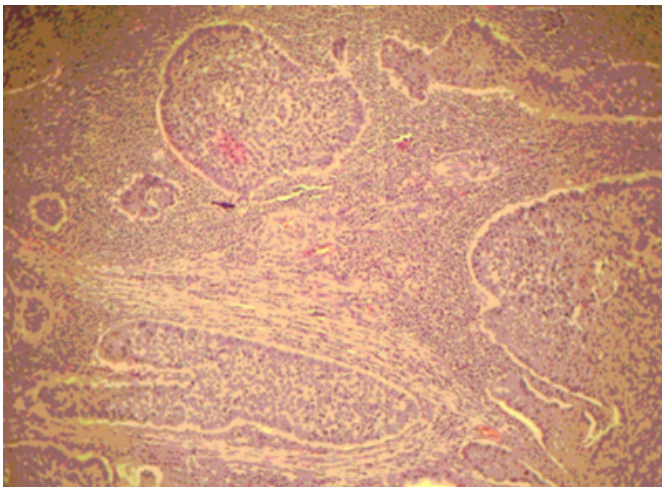
Figure 2: Adjacent squamous epithelium (10X, hematoxylin and eosin stain)



Underlying stroma showed a tumor composed of malignant cells arranged in clusters, trabeculae, insular pattern, and solid sheets. The cells showed pallisading at the periphery of the clusters (Fig. 3).

Figure 3

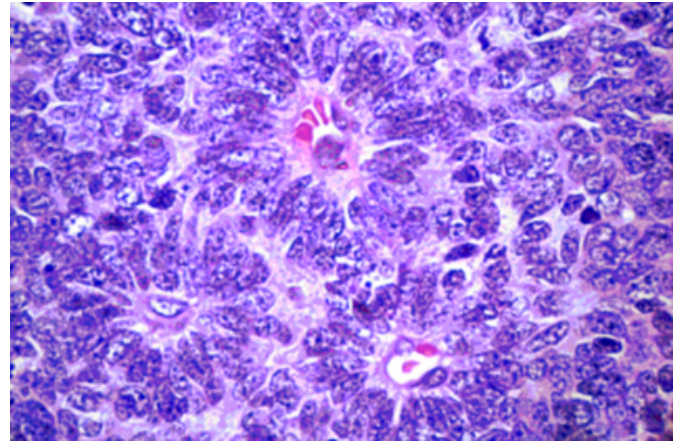
Figure 3: Insular pattern peripheral palisading (10X, hematoxylin and eosin stain)



Clear cleft like retraction spaces were seen around the cell clusters. At some areas the cells were arranged around blood vessels. At several foci the cells formed numerous rosettes and pseudo rosettes (Fig. 4).

Figure 4

Figure 4: Perivascular pseudo rosettes (40X, hematoxylin and eosin stain)



The cells showed moderate cytoplasm with oval to round nuclei with mild pleomorphism and fine to coarse chromatin. Atypical mitotic figures were observed. The criterion used to diagnose the disease entity was, a tumor of the uterine cervix composed of relatively uniform medium to large cells exhibiting neuroendocrine differentiation apparent by light microscopy, as evidenced by trabecular or insular arrangements of the cells, eosinophilic cytoplasmic granules of the type seen in neuroendocrine cells, or both of these features⁴. Thus the histopathological diagnosis was “large cell type of neuroendocrine cancer of uterine cervix and surgical margins free of tumor.”

Because of the histopathology report, she was referred for radiotherapy. She received both brachytherapy and teletherapy along with adjuvant chemotherapy. Three months after surgery she was doing well.

DISCUSSION

Large cell neuroendocrine carcinoma (LCNEC) of the uterine cervix is a rare malignancy that is highly aggressive and usually results in unfavorable outcomes. They are rarely discovered on routine Pap smear due to the submucosal location of the tumor with intact overlying mucosa in its earlier stages. The 5-year survival rate is around 14-39%, similar to that of the small cell type⁵.

Carcinogenesis: It is generally accepted that integration of high risk HPV into the host genome is the single most important event in the evolution of cervical cancer⁶. Integration of high risk HPV, in particular type 16 and to a lesser extent type 18, is associated with large cell neuroendocrine carcinoma of the uterine cervix^{6,7,8}. The demonstration of high risk HPV integration is an almost

ubiquitous finding in most cervical carcinoma subtypes, yet LCNEC is an uncommon variant despite its confirmed association with HPV16. The most remarkable aberration is found in chromosome 3₆₉.

Clinical Presentation: Early cases are asymptomatic. Usual presentation will be irregular vaginal bleeding₂, postcoital vaginal spotting and sanguineous vaginal discharge. Pelvic examination may reveal either cervical erosion or a cervical growth.

Classification: In 1996, a workshop was convened under the auspices of the College of American Pathologists and the National Cancer Institute to clarify the issues of classifying NEC₃₁₀₁₁. A new classification was proposed that encompasses four entities: typical (classic) carcinoid tumor, atypical carcinoid tumor, large cell neuroendocrine carcinoma and small (oat) 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. Neuroendocrine differentiation is demonstrated with pan-neuroendocrine markers such as chromogranin A, synaptophysin and neuron specific enolase. It is quite possible that LCNECs are frequently misdiagnosed as poorly differentiated squamous cell carcinomas or poorly differentiated adenocarcinomas, based upon the identification of focal areas of squamous or glandular differentiation, respectively₃₆₁₂. In such cases, the subtle neuroendocrine features of the large cell neoplasm are easily overlooked, but neuroendocrine markers would help. A variety of other peptides and hormones have been identified, but their clinical and diagnostic significance is limited.₅ Though these special neuroendocrine stains are useful for diagnosis, these could not be performed due to logistic reason in this particular case.

Histopathological criteria for the diagnosis of NEC of uterine cervix are listed in table 1.

Figure 5

Table 1: Histopathological Criteria for the diagnosis of NEC of uterine cervix

NEC (WHO ICD-O codes)	Cytological features	Mitosis	Necrosis
Classical carcinoid (8240/3)	No cytological atypia	Rare	None
Atypical carcinoid (8249/3)	Cytological atypia	≤10 MF/HPF	Focal
Large cell neuroendocrine carcinoma (8013/3)	Large cells with large vesicular nuclei and prominent nucleoli	>10 MF/HPF	Geographic
Small cell carcinoma (8041/3)	Small round cells with minimal cytoplasm	Abundant	Extensive
MF=mitotic figures; HPF=high-power field			

Differential diagnosis: It may be difficult to differentiate neuroendocrine cancer from non-neuroendocrine undifferentiated carcinoma, adenocarcinoma with neuroendocrine features, metastatic neuroendocrine carcinoma or undifferentiated sarcoma₅.

Treatment: Early-stage large cell neuroendocrine tumors of the cervix are aggressive. Multimodal therapy should be considered at the time of initial diagnosis. Based on the rarity of cervical neuroendocrine tumors, it is difficult to perform large-scale randomized control trials to delineate the optimal therapy. Therefore, the basis for treatment of large cell neuroendocrine tumors is derived from therapy for small cell cervical carcinoma and small cell lung carcinoma₂₃. Even in case of pulmonary LCNEC, the incidence, prognosis, and optimal treatment remain to be determined₇₁₃₁₄.

The treatment guideline for small cell neuroendocrine tumor can be used for the treatment of LCNEC, which is as follows. For localized operable cancer, radical hysterectomy with LN dissection and adjuvant chemo-radiotherapy; for locally advanced cancer limited to the pelvis, concurrent chemo-radiotherapy; and for metastatic cancer, palliative chemotherapy. Cisplatin (60-75 mg/m₂) plus etoposide (80-120 mg/m₂/day for 3 to 5 days) or paclitaxel is the most commonly used chemotherapy. Other regimens may include Carboplatin (AUC 5-6), Irinotecan (50-60 mg/m₂),

Cyclophosphamide, Doxorubicine, or Vincristine in different combinations.

CONCLUSION

Our case study reports that LCNEC may present as a bleeding cervical polyp. It should be interpreted carefully on histopathology so that it is not misdiagnosed as poorly differentiated carcinoma of cervix. Since LCNEC is an aggressive tumor multimodality treatment is advised in an attempt to reduce mortality.

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