Diagnosis of Small Cell Neuro-Endocrine Carcinoma Of Cervix

Dr. Bhushan Malhari Warpe,
Asst. Prof. Dept. of Pathology, Grant Government Medical College, Mumbai.
Email id- bhushan.warpe@gmail.com

Abstract:
There are several differences between neuroendocrine and other types of cervical cancer, in prognosis, diagnosis and treatment. Neuroendocrine cancer of the uterine cervix is a rare and aggressive disease. Small cell carcinoma is classified as a neuroendocrine tumor in the currently used World Health Organization histological classification of tumors of the uterine cervix (2003). Small-cell carcinoma is one of the most aggressive, poorly differentiated, and highly malignant neuroendocrine tumors and includes small-cell lung cancer and extrapulmonary small cell carcinoma (EPSCC). EPSCC is a rare disease, accounting for 2% of all small cell carcinoma. Because of the rare nature of this disease, clinical trials for neuroendocrine cancer of the cervix are lacking. Social media and other innovative techniques may be useful to identify patients with this rare tumor. Patients may benefit from receiving care from centers with expertise in treating this disease. Treatment for neuroendocrine cervical cancer is usually more intensive than that for most other types of cervical cancer and therapy often utilizes multiple different modalities such as surgery, chemotherapy and radiation.

Keywords:
Cervical cancer; Small cell neuro-endocrine carcinoma

1. INTRODUCTION:
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 (i.e. carcinoid and atypical carcinoid) is morphologically and clinically distinct from high-grade neuroendocrine carcinoma (i.e., 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 [1].

Well and poorly differentiated neuroendocrine tumors are grouped together only because of generic neuroendocrine marker expression (i.e. expression of the markers synaptophysin and chromogranin detected by immunohistochemistry). The biology and clinical outcome of poorly differentiated neuroendocrine carcinomas, however, are vastly different from the well differentiated neuroendocrine tumors. In fact, poorly differentiated neuroendocrine carcinoma likely possesses a non-neuroendocrine cell lineage and is more closely related to a de-novo carcinoma.

In recent years only, there has been an increased reported incidence of neuroendocrine tumors, which may reflect improvements in standardized classification criteria, and increased diagnostic recognition [2]. Neuroendocrine tumors primary to the gynecologic tract are still considered to be uncommon, with limited prospective data from which to guide decisions. The goal of this manuscript is to provide an insight on this gynecologic neuroendocrine tumors and a platform from which to evaluate the available treatment options for these challenging cases.

2. CASE REPORT:
A rich 49-year-old lady, P3L3 came with the chief complaint of irregular bleeding per vaginum since six months. There was history of post-coital bleeding on and off since six 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, thyroid disorder, diabetes mellitus, hypertension. She was addicted to smoking since last 15 years. Her vitals were stable. There was no lymphadenopathy.

Per speculum examination revealed a cauliflower growth, about 4 × 3 cm in sizes on the anterior lip of cervix. Her vagina appeared normal. 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 was made. Patient was admitted and prepared for cervical biopsy. Cervical smear for human papilloma virus (HPV) detection and typing along with the biopsy from cervical growth was taken. Patient was discharged with advice to follow-up with histopathology report. After ten days, she reported with histopathology report showing ‘small-cell neuroendocrine carcinoma of cervix’ (Figure 1).

The histopathologic diagnosis was confirmed with immunohistochemistry (IHC), which showed synaptophysin-positive (Figure 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. Also CD-56 was negative in our case.

3. DISCUSSION:

Neuroendocrine tumors (NETs) are neoplasms that are composed of cells which have features of both the endocrine (hormonal) as well as the nervous system [1]. They can be classified as benign or malignant. These tumors can originate from many different sites in the body, including the uterine cervix. The following discussion will be limited to malignant neuroendocrine carcinoma (NEC) of the cervix.

There are multiple different types of cervical cancer, named after the appearance of the cells under the microscope. The most common type is squamous cell cancer, accounting for 70% of all cervical cancers. The second most common is adenoocarcinoma, which accounts for 20-25% of all cervical cancer [3]. Neuroendocrine tumors account for only 2% of all cervical cancers [4].

Four subtypes of NEC have been delineated:

• Small cell neuroendocrine carcinoma
• Large cell neuroendocrine carcinoma
• Typical carcinoid tumor
• Atypical carcinoid tumor

Of these four types, carcinoid tumors, although malignant, are considered to be well differentiated and therefore have a more indolent course and favorable prognosis [1]. Poorly differentiated, or high grade, NEC includes small cell neuroendocrine carcinoma (SCNEC) and large cell neuroendocrine carcinoma (LCNEC). Of the four subtypes, SCNEC is most common and LCNEC second most common of NEC arising from the cervix [5].
Microphotograph-Malignant small dark round to angular cells, arranged either in nests or individually with nuclear moulding and overlapping (H&E, x 400). *Inset* reveals these tumor cells showing mildly pleomorphic hyperchromatic nuclei varying from round to angular with finely granular chromatin and indistinct nucleoli. (H&E, oil x 1000).

**Figure 1:**

Microphotograph- Malignant small round to angular cells with nuclear moulding and overlapping with cytoplasmic positivity (Synaptophysin, x 400). *Inset* reveals these tumor cells showing cytoplasmic positivity which stained the cytoplasmic neuro-secretory granules of the tumour cells (Synaptophysin, oil x 1000).

**Figure 2:**

However most of the neuroendocrine cancers of the cervix are small cell carcinomas, which account for up to 2% of cervical carcinomas [6]. They are characterized by high mitotic rate, extensive necrosis, frequent lymphovascular space involvement (LVS1) and a strong association with HPV-18.2 Though, our case was negative for HPV infection, it was 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 like in our case.
Because NEC of the cervix is uncommon, the etiology and predisposing risk factors are poorly understood. In one study, when compared to women with the more common squamous cell carcinoma of the cervix, women were slightly younger at the time of diagnosis. The mean age at diagnosis was 49 years-old (compared to 52 years-old). There was also a higher proportion of Asian women with NEC of the cervix, when compared to women with squamous cell carcinoma of the cervix [7].

While the Human Papilloma Virus (HPV) and smoking are now well-known risk factors for developing most other kinds of cervical cancer, less is known about the role they play in development NEC of the cervix. Several studies have demonstrated a relationship between HPV infection and NEC of the cervix [8]. However, unlike HPV-associated squamous and adenocarcinoma of the cervix which have a preinvasive lesion that can often be detected by routine screening methods prior to growth of an actual cancer, no such preinvasive phase appears to exist for NEC.

In general, the symptoms of neuroendocrine cancer do not appear to differ significantly from those of other types of cervical cancer [9]. Like other cancers of the uterine cervix, the symptoms of NEC of the cervix typically depend on the extent of the spread of disease (stage of disease). However, because of the aggressive nature of these tumors, patients more frequently have advanced disease at the time of initial diagnosis.

Similar to other cervical cancers, symptoms may include vaginal discharge, abnormal vaginal bleeding including postcoital bleeding (bleeding after intercourse), and pelvic pain. More advanced disease can include symptoms of weight loss, abdominal bloating, or symptoms specific to metastatic disease (liver, adrenals, bone, bone marrow, and the brain) [10].

Occasionally, like neuroendocrine tumors of the lung, small cell cancer of the cervix can present with paraneoplastic syndromes affecting the endocrine (hormonal) and/or nervous systems such as hypercalcemia (elevated blood calcium levels), neurologic disorders, Cushing’s syndrome, and SIADH [11]. Symptoms such as those listed above often prompt a medical evaluation leading to the diagnosis. Sometimes, routine gynecologic pelvic exam may reveal a cervical mass. Biopsy should be performed of any cervical mass to determine a more definitive cause and if possible, IHC too.

The diagnosis of small cell carcinoma of the uterine cervix by pathological examination includes small cell non-keratinizing squamous cell carcinoma, lymphoma, poorly differentiated adenocarcinoma. Presence of squamous architecture or glandular structure can separate small cell carcinoma from squamous cell carcinoma or adenocarcinoma. Nuclear moulding, indistinct nucleoli and tumor cell cannibalism can distinguish small cell carcinoma from lymphoma. In addition, immunocytochemical staining is a useful tool that gives an accurate diagnosis of small cell carcinoma of the uterine cervix. In our case, immunohistochemical staining was performed by neuroendocrine marker of Synaptophysin which was positive in our sections. So the other neuro-endocrine markers were not applied. CK-PAN was negative in our case ruling out epithelial origin of the tumour. Although a recent study revealed that CD56 is the most sensitive marker for diagnosis of small cell carcinoma of the uterine cervix and shows a more obvious diffuse reactivity pattern [12], the result of CD56 in our case was negative.
Early stage of disease 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 [13]. 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 [14]. Smoking has been linked to a worse clinical outcome for small cell cervical cancer like in our case. Small-cell cervical cancers have a reported 5-year survival of 36%.

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 non-small-cell lung cancer, is another potential target. The Hedgehog pathway and Bcl-2 represent other areas of investigation [14].

Like most cancer, the prognosis depends on the stage of disease at the time of diagnosis. In one study of women with NEC of the cervix, 71% of patients were diagnosed with early stage disease (stage I-IIA), 24% were diagnosed with locally advanced disease (stage IIB-IVA), and 4% with diagnosed with distant metastatic disease (stage IVB) [9]. Our patient was in early stage of the malignancy.

When looking at patients diagnosed at all stages, five year survival for NEC of the cervix is worse than that for other more common types of cervical cancer (36 vs 60-70%) [15]. In the same study mentioned above, 5-year survival was 37% for those with I-IIA disease versus 9% for those with more advanced disease. In another series, survival for stage I was 42%, stage II 19%, stage III 10% and stage IV 23% [7].

It appears that prognosis for small cell neuroendocrine carcinoma originating from the cervix is better than when originating in the lung. As noted above, while the five year survival for patients with early stage NEC of the cervix ranges from 19-42%, the survival for limited stage lung cancer is about 10%. Similarly, the survival for those with extensive stage disease of the cervix is about 10-23%, while the comparable survival rates for disease starting in the lung is 1-2% [16].

4. CONCLUSION:

Small cell neuro-endocrine carcinoma of the uterine cervix is a rare tumor but has an aggressive clinical course and poor prognosis because of frequent metastases occurring at an early stage. Thus it is important to differentiate small cell carcinoma of the uterine cervix from other malignant tumors of the cervix. It is closely related to pulmonary small cell carcinoma and is generally managed with a multimodality approach. Morphological features, cytopathology and histopathology play important roles in making an accurate diagnosis and IHC tests can offer additional
useful assistance. Rather than using panel of IHC markers just Synaptophysin and CK-PAN are enough for its diagnosis to avoid costs. Currently, due to the rarity of the disease, there are no clinical trials available for the treatment of women that are specific to neuroendocrine carcinoma of the cervix. The latter can be done by making regional detection and management centers for such patients.

5. REFERENCES:


