

Large cell neuroendocrine carcinoma of cervix: A case report

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ABSTRACT

Neuroendocrine carcinoma of the cervix is a rare aggressive tumor with a poor prognosis. Neuroendocrine carcinomas account for 1–1.5% of cervical cancer and around 12.5% were of large cell types. We report the case of a 55-year-old woman who came with complaints of pain abdomen and was reported as large cell neuroendocrine carcinoma of the cervix on biopsy. Immunohistochemistry was done which confirmed the diagnosis.

Key words: Cervix, Large cell neuroendocrine carcinoma, Neuroendocrine tumor

Neuroendocrine tumors (NETs) are derived from neuroendocrine cells present in various parts of the body. These cells are derived from embryonic neuroectoderm which shows a similar immunohistochemical profile to the endocrine glandular cells [1]. They have been classified as well-differentiated NETs and poorly-differentiated NETs. Large cell neuroendocrine carcinomas are poorly differentiated NET. Neuroendocrine carcinomas account for 1–1.5% of cervical carcinomas [1], out of which 12.5% accounts for large cell type [2]. Histological criteria for the diagnosis of large cell neuroendocrine carcinoma of the cervix are the presence of large cells with abundant cytoplasm, vesicular nuclei with prominent nucleoli, and high mitotic rate. The growth patterns of tumor cells are organoid, trabecular, insular, or solid pattern, often showing peripheral palisading or rosette-like arrangement. Immunohistochemical markers for diagnosing NETs are chromogranin, synaptophysin, CD 56, and neuron-specific enolase (NSE).

In our case, the tumor cells had vesicular nuclei with nucleoli and a moderate amount of cytoplasm. They were positive with synaptophysin and had high mitotic activity (Ki 67 labeling index was >72%). We report this case of large cell neuroendocrine carcinoma due to its rarity of occurrence in the cervix.


CASE REPORT

A 55-years-old female presented with complaints of pain in the lower abdomen and post-menopausal bleeding of 1-month duration. Per speculum examination revealed hypertrophied

cervix. Ultrasound abdomen showed bulky cervix. There was no evidence of a mass lesion in the cervix. The shape and echotexture were normal. Magnetic resonance imaging revealed a subcentimeter nabothian cyst in the cervix. No obvious growth was noted in the cervix. Hematological parameters were within normal limits.

A cervix biopsy was performed and sent for histopathological examination. Immunohistochemistry and morphology favored the diagnosis of neuroendocrine carcinoma. Later, radical hysterectomy with bilateral salpingo-oophorectomy was performed. We received uterus with cervix measuring 6.5 cm × 4.5 cm × 2.5 cm along with attached vaginal cuff. Cut section of cervix showed nabothian cyst. No growth was identified. Cut section of uterus showed endometrium measuring 0.3 cms in thickness, myometrium measuring 1.5 cms in thickness. The right and left fallopian tubes were measuring 4 cms each. The right ovary was measuring 2.3 cm × 1.5 cm × 1 cm and the left ovary was measuring 2.5 cm × 2 cm × 1.5 cm. The cut section of the ovaries and fallopian tube were normal. The right and left pelvic lymph nodes were also received which showed reactive hyperplasia.

Microscopic examination of the cervix revealed ectocervix lined by stratified squamous epithelium showing surface dysplasia in transition to infiltrating lesion. The lesion was composed of polyhedral cells arranged in lobules separated by fibrous septa with rare acinar formations (Fig. 1a and b). Tumor cells showed nuclear pleomorphism, salt and pepper-like chromatin, and nucleoli in some of the cells. They had a scant to moderate amount of cytoplasm (Fig. 1c). Many atypical mitotic figures were seen. Perineural infiltration, lymphatic and vascular tumor emboli were

Access this article online	
Received - 27 February 2022 Initial Review - 12 March 2022 Accepted - 26 March 2022	Quick Response code 
DOI: 10.32677/ijcr.v8i4.3355	

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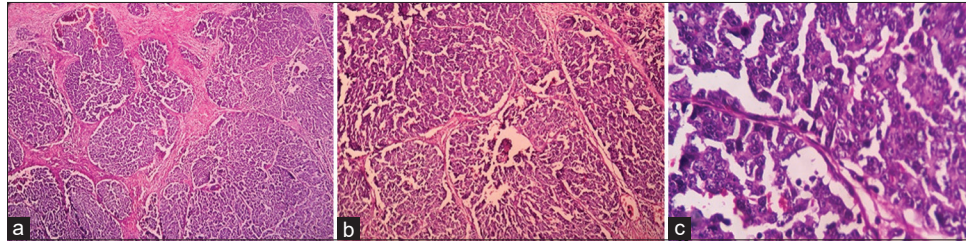


Figure 1: (a) Histopathological examination showing (a) Lesion composed of polyhedral cells arranged in lobules separated by fibrous septa with rare acinar formations (H&E ×50); (b) Lesion composed of polyhedral cells arranged in lobules separated by fibrous septa (H&E ×100); (c) Tumor cells showing nuclear pleomorphism with granular chromatin and prominent nucleoli (H&E ×400)

also present. The tumor showed a stromal invasion of 0.7 cm and the horizontal extent of the tumor was 0.8 cm. The pathological stage of the tumor was pT2aN0.

Immunohistochemistry was performed. Tumor cells showed moderate cytoplasmic positivity with synaptophysin (Fig. 2) and negative for chromogranin A. Ki 67 index was $\geq 70\%$. These findings confirmed the diagnosis of large cell neuroendocrine carcinoma (poorly differentiated/high grade). Postoperatively, the patient's condition was uneventful and later, she received six cycles of chemotherapy with carboplatin 625 mg and etoposide 150 mg.

DISCUSSION

Cervical NETs are rare aggressive malignancies, prone to early metastasis. Among NETs, large cell neuroendocrine carcinomas are still rare and approximately, only 70 cases are reported in the literature [3]. The cell of origin for the NETs is neurosecretory cells present in various organs of the body. Most commonly, they are found in the gastrointestinal tract and the lung. Albores-Saavedra *et al.* (1972) first described the neuroendocrine neoplasm in the cervix [4]. In 1997, the terminology for uterine cervical NETs was proposed at the workshop by the National Cancer Institute and the College of American Pathologists and is similar to the pulmonary NETs [5]. Precursor cells for NETs in the cervix were thought to be argyrophilic cells in the ectocervix and ectocervical epithelium [6]. Grayson *et al.* had suggested that there is a potential association between human papillomavirus infection and large cell neuroendocrine carcinoma of the cervix [7].

Among NETs of the cervix, small cell neuroendocrine carcinoma of the cervix is more common than well-differentiated NETs (typical carcinoid NET G1 and atypical carcinoid NET G2) which are rare in the cervix [8]. The grading of neuroendocrine carcinomas in the cervix is the same as in other locations like the lung and gastrointestinal tract.

Morphological features of large cell neuroendocrine carcinoma described by the World Health Organization (WHO) in 2015 are large cell size with trabecular, organoid, nesting, and palisading rosette pattern with the high mitotic rate ($>10/2 \text{ mm}^2$), low nuclear to cytoplasmic ratio, vesicular or fine chromatin and necrosis. Tumor cells will be positive for synaptophysin, chromogranin, CD 56, and less specific for NSE.

Very few studies are available in the literature on the common site for NET metastasis. Some studies on the epidemiology of

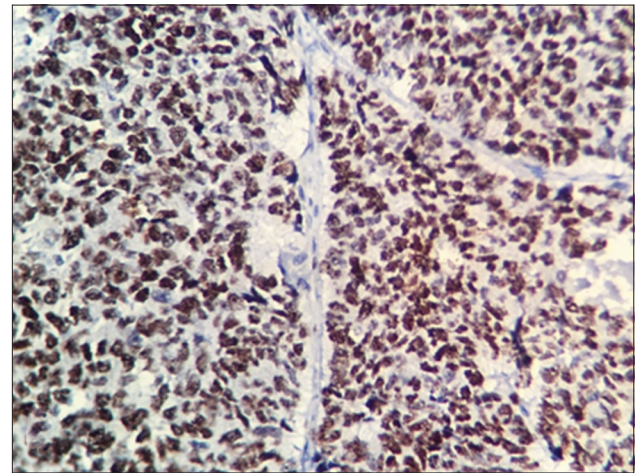


Figure 2: Immunohistochemistry showing tumor cells showing moderate cytoplasmic positivity with synaptophysin (synaptophysin ×400)

metastasis in cervical large cell neuroendocrine carcinoma have reported that it has an aggressive behavior with early metastasis to surrounding lymph nodes, liver, bone, and brain [9]. Due to the rarity and aggressiveness of the tumor, optimal treatment for large cell neuroendocrine carcinoma has not been clearly described. The Gynecologic Cancer Intergroup reviewed the treatment for small cell neuroendocrine carcinoma in 2014 and recommended chemotherapy and radical surgery for patients in the early stage. For the advanced stage patients and patients with recurrence, chemotherapy with etoposide, cisplatin, paclitaxel, and bevacizumab was recommended [10]. Embry *et al.* in their multivariate analysis have shown that the incorporation of chemotherapy at any stage of carcinoma was associated with longer survival. However, the early disease stage was associated with a better prognosis and the overall survival period of advanced stage IV cancer was approximately 1.5 months [11]. Neuroendocrine carcinoma invades lymphovascular space and has poor prognosis than squamous cell carcinoma and adenocarcinoma of the cervix. The 5-year survival rate of neuroendocrine carcinoma is around 30% when compared to more than 65% for adenocarcinoma and squamous cell carcinoma [12].

CONCLUSION

Large cell neuroendocrine carcinoma is a rare aggressive malignancy of the cervix which is misdiagnosed often and is associated with a poor prognosis. Due to the rarity of cervical

neuroendocrine carcinoma, optimal treatment has not been established but can be treated effectively with a multimodality regimen including radical surgery and platinum-based chemotherapy on early diagnosis. Hence, it is important to consider neuroendocrine carcinoma as a differential diagnosis of cervical malignancies which will help to identify and provide treatment at an earlier stage.

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Funding: None; Conflicts of Interest: None Stated.

How to cite this article: Vissa S, Rukmangadha N, Kumar VS. Large cell neuroendocrine carcinoma of cervix: A case report. *Indian J Case Reports*. 2022;8(4):88-90.