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Case Report

Exploring neuroendocrine carcinoma of the cervix: a case report and literature review

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ABSTRACT

Neuroendocrine neoplasms (NENs) are rare, comprising less than 1% of cervical malignancies. Diagnosis and management of cervical neuroendocrine carcinoma (NEC) pose challenges due to its rarity and aggressive nature. Aim of the study was to highlight the importance of considering NEC in the differential diagnosis of cervical malignancies and underscore the potential benefits of comprehensive treatment approaches. We report a case of a 35-year-old woman presenting with post-coital bleeding, subsequently evaluated and diagnosed with NEC T1b1N0Mx following radical hysterectomy. Adjuvant chemoradiotherapy and chemotherapy led to one year of remission. Cervical NEC poses diagnostic and therapeutic challenges due to its rarity and aggressive nature. Despite multimodal treatment, prognosis remains poor, warranting further research and targeted therapies. The rarity of cervical NEC emphasizes the need for increased awareness among clinicians to facilitate early detection and appropriate management. Further studies are warranted to explore novel treatment modalities and improve outcomes for patients with this challenging malignancy.

Keywords: Carcinoma cervix, Immunohistochemistry, Neuroendocrine neoplasia, Cervix

INTRODUCTION

Neuroendocrine neoplasms (NENs) arise from neuroendocrine cells, commonly found in the gastrointestinal tract, pancreas, and lungs.[1] These cells originate from the embryonic neuroectoderm and exhibit an immunohistochemical profile similar to endocrine cells. NENs may secrete hormones, termed functional, while those that do not are considered non-functional.[2] Well-differentiated NENs are categorized as low-grade tumors, with grade 1 (typical carcinoid) and grade 2 (atypical carcinoid) based on cell proliferation and mitotic index. Poorly differentiated NENs are high-grade tumors, mainly presenting as small-cell carcinoma or large-cell carcinoma. The terminology includes carcinoid, neuroendocrine tumor (NET), and well-differentiated NEC for well-differentiated NENs, and small cell and large cell NEC for poorly differentiated NENs.[3] NENs of the cervix, first reported in the 1970s, now comprise about 0.9-1.5% of cervical malignancies, with small cell NEC being predominant.[4] These tumors tend to metastasize early, leading to a poor prognosis. They are frequently associated with human papillomavirus (HPV) infection, implicated in their development.[5] Mean recurrence-free survival is approximately 16 months, while mean overall survival is estimated at 48 months.[6] Early and accurate diagnosis is crucial due to the aggressive nature, poor prognosis, and the need for specific treatment modalities. Here, we present a case of a neuroendocrine tumor in a young female, highlighting its rarity.

CASE REPORT

A 35-year-old woman, with one previous pregnancy, presented to the gynecology outpatient department complaining of intermittent post-coital bleeding over the

course of a year. Her menstrual history was otherwise unremarkable. Upon speculum examination, a 1×1 cm lesion was identified on the posterior lip of the cervix, prompting further investigation with colposcopy and guided biopsy due to suspicion of a high-grade lesion. The upper vagina appeared normal, with no abnormal findings noted during vaginoscopy. A per vaginal rectal examination revealed a normal uterus, a firm cervix, free parametrium and rectal mucosa.

The biopsy results indicated HPV-associated poorly differentiated squamous cell carcinoma, leading to a clinical diagnosis of cervical carcinoma, international federation of gynaecology and obstetrics (FIGO) stage IB1. Subsequent magnetic resonance imaging (MRI) findings suggested chronic cervicitis, with normal results observed in the parametrium, pelvic side walls, and abdominal organs.

The patient was scheduled for a type c radical hysterectomy with bilateral salpingo-oophorectomy and bilateral pelvic lymphadenectomy. Gross examination of the hysterectomy specimen revealed a growth measuring 1.5×1.5×1 cm on the posterior lip of the cervix (Figure 1), positioned 2.0 cm from the resected end of the vagina, 3 cm from the right parametrium, and 2 cm from the left parametrium (Figure 2). Both the intraoperative and postoperative periods were uneventful. The final histopathology report confirmed NEC (Figure 3) T1b1N0Mx, indicating deep stromal invasion and lymphovascular space invasion, with positive immunohistochemistry results for p16, synaptophysin, (Figure 4) and pan CK. Following the discussion in the tumor board meeting, the patient was planned for adjuvant chemoradiotherapy and chemotherapy, consisting of 4 cycles of cisplatin and etoposide followed by concurrent chemoradiotherapy. The patient completed her chemoradiotherapy regimen and has remained in remission for one year, undergoing regular three-month follow-ups.

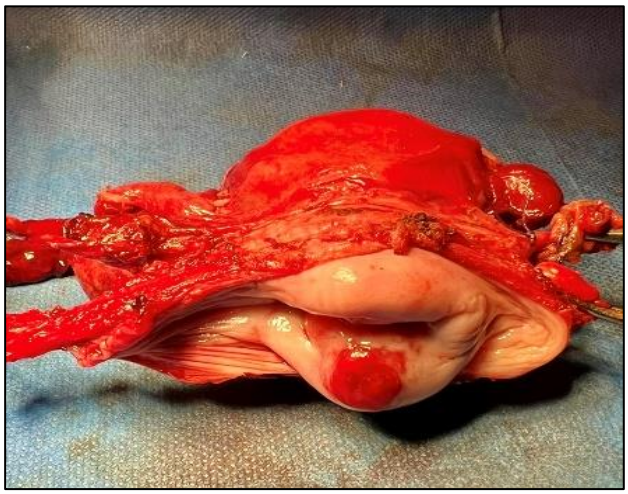

Figure 1: Radical hysterectomy specimen showing growth over posterior lip of cervix.

Figure 2: Radical hysterectomy specimen with uterus, cervix, part of vagina, bilateral tubes and ovaries along with bilateral parametrium.

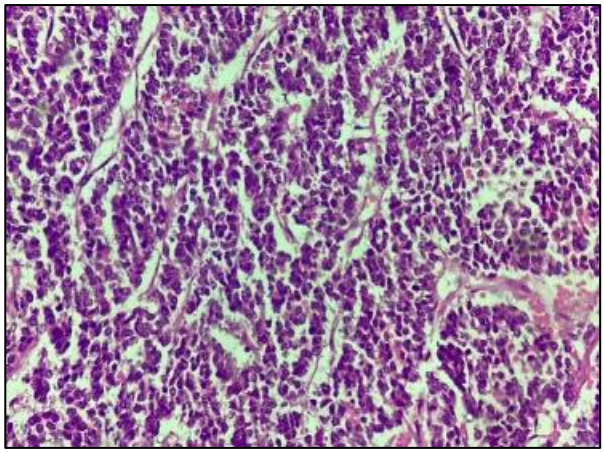

Figure 3: Invasive tumor comprising of sheets of small cells with scant cytoplasm, hyperchromatic nuclei with fine granular chromatin, nuclear molding suggestive of neuroendocrine tumor (400x).

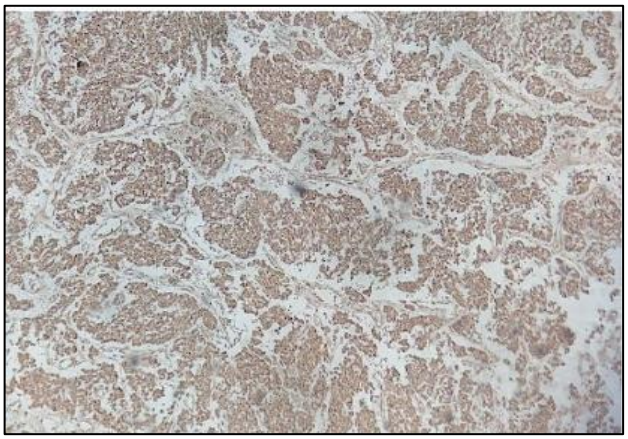

Figure 4: Tumor cells exhibit positive cytoplasmic expression for synaptophysin (100x).

DISCUSSION

NEC is a rare and aggressive malignancy, commonly found in the lungs and gastrointestinal tract. NENs of the cervix were first reported in 1970, with their precise origin still uncertain, although argyrophilic cells in the cervix epithelium are considered potential precursors. Small cell NEC (SCNEC) is the predominant subtype, accounting for 80% of cases, and represents less than 1% of all female genital tract malignancies. Diagnosis of SCNEC typically occurs around the age of 48.1 years.[7] These tumors are prone to early lymphatic and hematogenous spread, posing a high risk of nodal metastases, even in cases clinically confined to cervix. In our case, a 35-year-old patient presented with a tumor strictly localized to the cervix, with no evidence of local or distant spread. The 2018 FIGO staging system incorporates imaging modalities such as computed tomography (CT)/MRI or PET/CT scan, along with pathological assessments, for comprehensive tumor staging.[8]

The histomorphological analysis presents a range of potential differential diagnoses, including poorly differentiated squamous carcinoma with small cells, poorly differentiated adenocarcinoma, low-grade endometrial stromal sarcoma, lymphoma, rhabdomyosarcoma, melanoma, myeloid sarcoma, and neuroectodermal tumor (NET).[9] According to McCluggage et al synaptophysin and CD56 are the most sensitive markers, while chromogranin is the most specific neuroendocrine (NE) immunohistochemical marker.[10] Initially, based on biopsy findings, our case was misdiagnosed as poorly differentiated squamous cell carcinoma. However, upon thorough histomorphological examination and immunohistochemistry (IHC) analysis in the final specimen, our case tested positive for synaptophysin, supporting a diagnosis of a neuroendocrine tumor.

According to Alejo et al 85% of NECs of the cervix are positive for human papillomavirus (HPV). They suggest that these tumors could potentially be prevented through the administration of prophylactic HPV vaccines.[5] Similarly, our case was also associated with HPV.

The management of neuroendocrine tumors (NETs) of the cervix involves a multimodal approach.[7] Early-stage disease typically warrants radical hysterectomy, followed by adjuvant concurrent chemoradiation and chemotherapy. Additionally, the utilization of immune checkpoint inhibitors has shown promise in the treatment of cervical NECs.[11]

In this case, adverse prognostic indicators included tumor stage, lymphovascular space invasion, and neuroendocrine histology. Despite employing a multimodal treatment approach, the prognosis remains unfavourable, with a five-year survival rate of 36% and a median overall survival ranging between 22 and 25 months.[7]

CONCLUSION

Cervical NEC presents diagnostic and therapeutic challenges due to its rarity and aggressive nature. Despite multimodal treatment, the prognosis remains poor. Further research into novel therapies is imperative. Increased awareness among clinicians is crucial for early detection. Accurate diagnosis and differentiation from other high-grade cervical carcinomas are paramount for optimal clinical care.

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