

Adenocarcinoma Admixed with Small Cell Neuroendocrine Carcinoma of the Uterine Cervix- A Case Report

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Abstract

Background: Among the unfamiliar tumours of uterine cervix, adenocarcinoma admixed with small cell neuroendocrine carcinoma (SCNEC) are of paramount importance; partially in fulfilling the primary goal of reaching an accurate diagnosis and more importantly determining the prognosis of this type of carcinoma as unequivocally, the prognosis is tremendously poor in this type of carcinoma. Other than this, the case is extremely rare throughout the world as documented by only few reports internationally till date.

Case Report: Here, we present a case of 35 years old female patient with cervical adenocarcinoma admixed with small cell neuroendocrine carcinoma (SCNEC). She underwent colposcopic biopsy initially for her complaints of lower abdominal pain and post coital bleeding for one month. This revealed an adenocarcinoma (papillary pattern), Grade-I. Finally, after Radical Wertheim hysterectomy, histological examination of specimens revealed two malignant components prevailing side by side. A part of it showed tumour cells arranged in tubulovillous pattern and papillary structure. Small foci show PAS positive material along the apical region. A second component is composed of small undifferentiated cells. These cells have small nuclei and granular chromatin with scanty cytoplasm. They are present in solid groups. Immunohistochemistry was performed for further confirmations.

Conclusion: If adenocarcinoma is detected in smears or colposcopic biopsy, further emphasis should be prioritized to rule out any component of SCNEC accomplished by complete histological and immunohistochemical analyses to resort to an accurate diagnosis.

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Key words: Adenocarcinoma, small cell neuroendocrine carcinoma

Introduction

According to WHO histological classification of tumours of the uterine cervix, squamous cell tumours and precursors consist of 70% and glandular tumours and precursors consist another 25%. All other varieties form only 5% of all uterine tumours. Neuroendocrine tumour is one of them. Among the uncommon

tumours of uterine cervix, adenocarcinoma admixed with small cell neuroendocrine carcinoma (SCNEC) are extremely rare but importance lies in the exact recognition because of the poor prognosis. Only a few cases have been reported internationally till date. Immunohistochemistry also aid in the diagnosis immensely.

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Case Report

We report a case of a 35-year-old woman admitted in BSMMU hospital, presented with lower abdominal pain and postcoital bleeding for one month. Her menstrual and obstetric history was unremarkable and she took OCP irregularly. Her VIA test was positive and colposcopy shows a large(3x3cm) cauliflower like growth present in cervix. Following colposcopic biopsy reveals an adenocarcinoma (papillary pattern), grade-I. Finally, after radical Wertheim hysterectomy, gross findings were:

- Tumour site: Cervix(anterior and posterior, left).
- Tumour description: Polypoid growth, cut surface- solid and gray white.
- Extent of tumour: Lower uterine wall.
- Vaginal cuff, parametrium and other organs are free of tumour.

Histological examination of specimens revealed two malignant components prevailing side by side. A part of it showed tumour cells arranged in tubulovillous pattern and papillary structure. Small foci revealed PAS positive material along the apical region of the villi and glands. A second component was made of small undifferentiated cells present in solid groups. These cells had small nuclei and granular chromatin with scanty cytoplasm. Immunohistochemistry findings were as follows:

- Pan CK +ve in both components
- CK7 +ve in adenocarcinoma
- Chromogranin +ve in smaller cells
- Synaptophysin +ve in smaller cells
- P16 overexpressed in both components

So, the histopathological diagnosis was 'cervical adenocarcinoma admixed with small cell neuroendocrine carcinoma (SCNEC).

Histologic findings of uterine cervical carcinoma

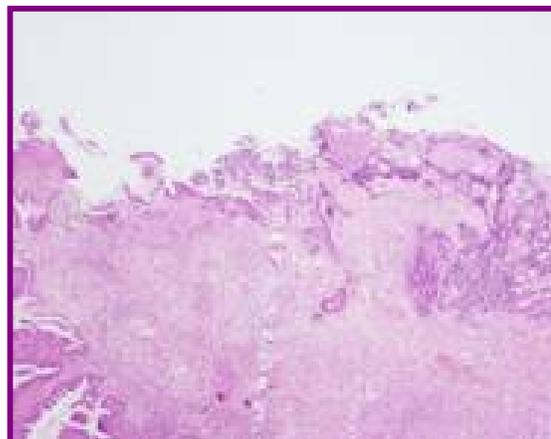


Figure 1. Initial punch biopsy containing undifferentiated cells

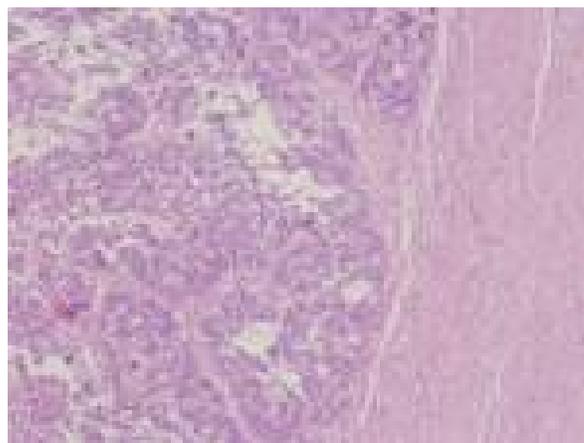


Figure 2. Small cell component

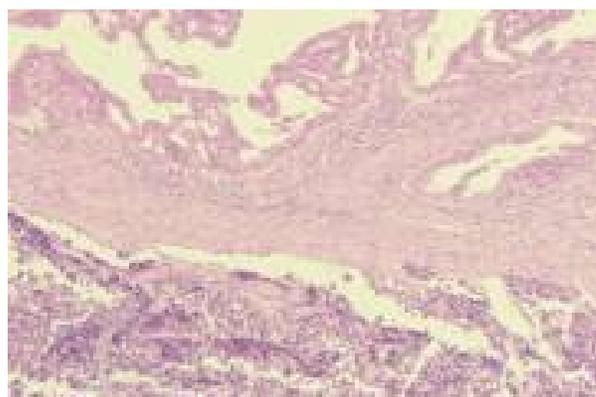


Figure 3. Both small cell and adenocarcinoma component



Figure 4. PAS stain of adenocarcinoma component

Immunohistochemistry



Figure 5. With CK7 shows SCNEC component is negative, Adenocarcinoma areas are positive

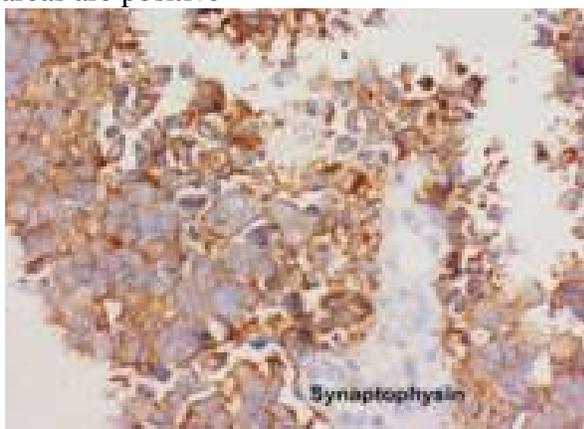


Figure 6. With synaptophysin shows both components are positive

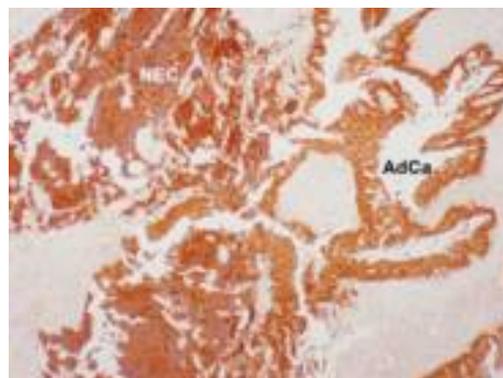


Figure 7. With p16 – both are positive

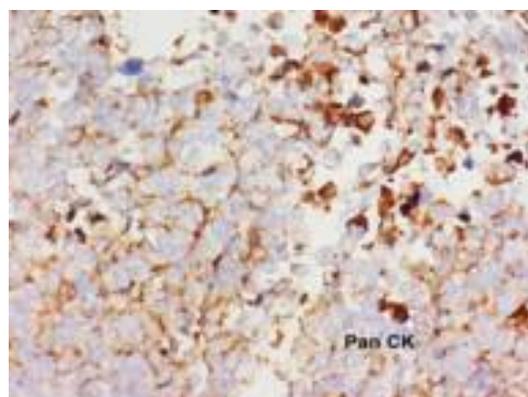


Figure 8. With Pan Cytokeratin – positive in each components

Discussion

Cervical neuroendocrine carcinomas (NECs) are categorized into two groups, i.e., low-grade neuroendocrine tumors such as typical carcinoid and atypical carcinoid and high-grade NECs such as small cell NEC (SCNEC) and large cell NEC.¹ SCNEC comprises approximately 2% of all cervical cancers and is highly aggressive with early nodal and distant metastases, often resulting in a poor prognosis.^{2,3} Most SCNECs present in a pure form, and only 4% of tumors are associated with adenocarcinoma.^{4,5} Cytological studies of SCNEC have been reported in eight cases to date; of these eight cases, one showed as SCNEC with adenocarcinoma in the uterine cervix.⁶ Even if the mixed-type is mainly

composed of neuroendocrine-differentiated cells, it is defined as adenocarcinoma admixed with SCNEC by the World Health Organization (WHO) criteria. This is further complicated by the coexistence of other carcinomas, such as squamous cell carcinoma *in situ* (SCIS), which may exhibit a cytological morphology similar to that of SCNEC.⁷

There are some evidences of strong relationship with human papillomavirus (HPV) type 16 and 18. As a result, vaccination against HPV16 and HPV18 might provide protection. Treatment option includes radical hysterectomy with bilateral lymphadenectomy, radiation & chemotherapy. 5-year survival is 30 - 40%; relapse in 2/3 at median 8 months. Paraneoplastic syndrome may occur and includes Cushing syndrome, carcinoid syndrome, SIADH and hypoglycemia. Prognostic factors are clinical staging, age at diagnosis, deep stromal invasion, baseline state of health, smoking etc.

In this report, we presented a rare case of adenocarcinoma admixed with SCNEC. According to the current WHO classification, tumors showing neuroendocrine differentiation in association with variants of cervical adenocarcinoma are defined as “adenocarcinoma admixed with NEC,” in which the prognosis is similar to that of cervical SCNEC.⁸ The cytological findings of this rare malignancy have been reported only a few times⁶ because sampling through brush tool is not adequate for detecting SCNEC cells, which tend to show a subepithelial cell growth pattern.[9] In our case, initial colposcopic diagnosis of adenocarcinoma of cervix was diagnosed as composite adenocarcinoma and small cell neuroendocinecarcinoma of cervix in Radical Wertheim Hysterectomy specimen.

During colposcopic biopsy examination, SCNEC may be missed in diagnosis as the entire tissue may not be representative for reaching in accurate diagnosis. Histologically, the tumor was comprised of two adjacent components containing either small-sized or moderately sized cells [Figure 1]. The smaller cells exhibited a scant cytoplasm, and their nuclei were either round or elliptical with nuclear molding. Tumor cells exhibited nuclear hyperchromasia and inconspicuous nucleoli. In contrast, the area with moderately sized cells was found to be composed of solid, papillary, and tubular patterns accompanied by amorphous material and necrotic debris [Figure 2]. These tumor cells harbored a thick cytoplasm, and the nuclei showed karyomegaly and were oval to elongated in shape, with prominent nucleoli.

Immunohistochemically, small cell neuroendocrine component can be confirmed by NSE (80%), chromogranin (60%), synaptophysin (70%), serotonin, CEA, p16, S100, keratin (variable). For adenocarcinoma, p16(Overexpressed in > 95% of cases - diffuse, strong nuclear and cytoplasmic staining), mCEA: 100% (any degree of staining) and CK7 can be used.

Conclusion

So, whenever adenocarcinoma is detected in smears or colposcopic biopsy, further emphasis should be prioritized to rule out any component of SCNEC accomplished by complete histological and immunohistochemical analyses to resort to an accurate diagnosis and prognosis.

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