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Uterine cervix mixed adenoneuroendocrine carcinoma: case report of a rare, high grade and aggressive tumor



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ABSTRACT

Introduction: Neuroendocrine carcinoma of the uterine cervix is a rare type of cancer in the female reproductive system, accounting for only about 1% of all malignancies in the uterine cervix. Mixed Adenoneuroendocrine Carcinoma (MANEC) is a combination of neuroendocrine components and non-neuroendocrine components, with each component contribute >30% of the tumor cells. This rare type of tumor is aggressive, high recurrence rates, and early distant metastases.

Case description: A 37-year-old female patient referred for evaluation after a previous finding of a cervix mass and a clinical diagnosis of cervical carcinoma IB2. Ultrasonography examination concluded a cervical mass, suspicious of malignancy. On macroscopic examination, it was found white-grey colored, huddle, and brittle mass filled the entire cervix with a size of 5 × 4 and 5 × 1 cm. Routine histopathological examination shows neoplastic cells forming a trabecular pattern, organoid, part with rosette formation, infiltrative

between the connective tissue and a large area of necrosis. These cells conform to a uniform morphology, small oval to round nucleus, partially composed of molding, narrow cytoplasm, salt and pepper chromatin, and mitotic figure > 25/10 HPF. At some other focus, neoplastic cells appear cribriform, solid, and tubular, with a round to oval hyperchromatic nuclei, increased N/C ratio, severe nuclear pleomorphism, eosinophilic cytoplasm, mitotic figure 5/10 HPF. The metastatic cell was found in four right pelvic lymph nodes, and five left pelvic lymph nodes. Immunohistochemistry examination of chromogranin-A and CEA shows positive, focal distribution on tumor cells cytoplasm. Synaptophysin shows positive, diffuse distribution on tumors cell cytoplasm. Ki-67 was positive in 90% malignant cell nuclei.

Conclusion: The result of clinical, radiological, routine histopathology, and immunohistochemical examinations support the pathological diagnosis of MANEC.

Keywords: aggressive, high grade, MANEC, uterine cervical

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INTRODUCTION

Neuroendocrine carcinoma of the cervix is a rare malignancy arising in the female reproductive system. It accounts for only about 1% of all female cervical malignancies. In general, it is divided into four categories: small cell, large cell, atypical cell, and classical carcinoid tumors. Among all categories, small cell neuroendocrine carcinoma has the highest incidence.^{1,2}

On the other hand, adenocarcinoma constitutes about 20% of all types of cervical cancer. Although, frequent screening has reduced the incidence of cervical cancer, particularly the invasive squamous cell carcinoma; it failed to detect adenocarcinoma precursor lesions. The average age of patients affected by adenocarcinoma is 50 years-old. Neuroendocrine carcinomas that are arising in the cervix assigned to similar terminology used in gastro-entero-pancreatic tumors. High-grade neuroendocrine carcinoma consists of high-grade malignant cells, and it can be small cells or large cells.^{2,3}

This case report presents a case of Mixed Adenoneuroendocrine Carcinoma (MANEC).

MANEC is a combination of neuroendocrine and non-neuroendocrine tumor cells. Components of neuroendocrine and non-neuroendocrine are apparent, where each of these components contributes >30% of the total tumor cells. Both can be found separately or mixed up. The incidence of MANEC is 1% of all uterine cervical malignancies.⁴⁻⁶

CASE REPORT

The patient was a 37 years old female who was referred to our tertiary-level hospital for further investigation of a cervical mass and clinical diagnosis of cervical carcinoma IB2. The ultrasonography examination reveals a cervical mass suspicious of malignancy and nodules in the left lobe of the liver, likely a metastatic origin. The gallbladder, spleen, pancreas, both kidney, and bladder did not show any abnormalities.

Surgery was performed, and the specimen was sent for pathology examination. The first specimens consist of vaginal cuff, cervix, uterus, right and left parametrium, right fallopian tube, and left adnexa.

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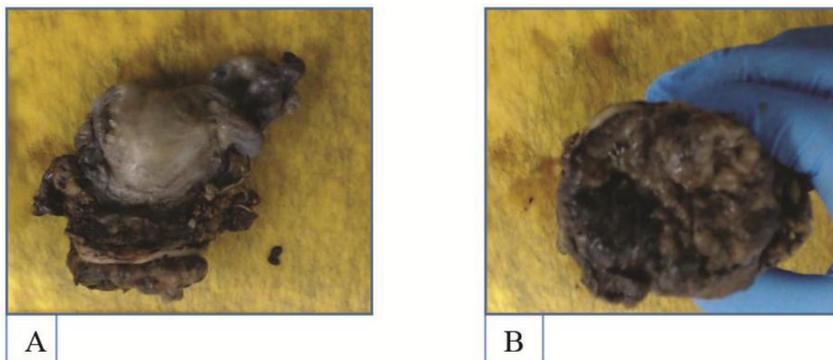


Figure 1 Gross appearance of the tumor. A. Vaginal cuff, cervix, uterus, right fallopian tube and left adnexa. B. The tumor filled the entire cervix

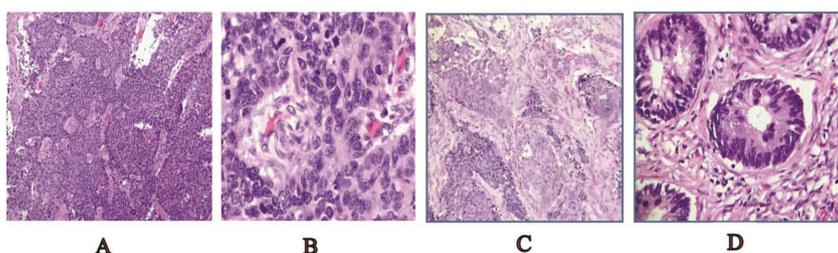


Figure 2 Microscopic image of the tumor. A. B. Neuroendocrine carcinoma components (A. HE, 40x, B. HE, 400x). C. D. Adenocarcinoma components (C. Cribriform pattern, HE, 100x; D. Tubular pattern, HE, 400x)

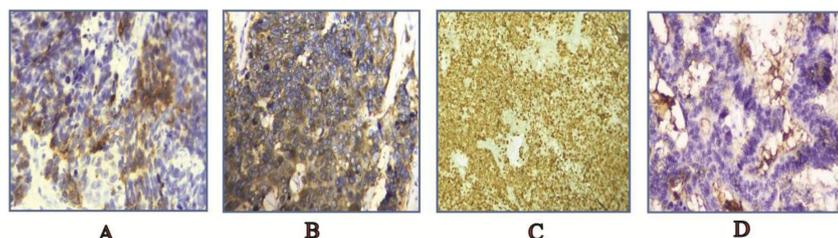


Figure 3 Microscopic image after immunohistochemistry staining. A. Chromogranin-A shows focal positive (patchy) in cytoplasmic cell tumors (CgA, 400x). B. Synaptophysin shows positively diffused in cytoplasmic cell tumors (Syp, 400x). C. Ki-67 shows positive in malignant cell nuclei > 90% (Ki-67, 100x). CEA shows positive focal in cytoplasm of tumor cells (CEA, 400x)

The mass was white-gray colored, huddle, and brittle. It fills the entire cervix with the estimated size was 5 × 4 and 5 × 1 cm. The second specimen from the right pelvic contains a piece of tissue measured about 4 × 3 × 2 cm and includes four lymph nodes. The third specimens from left pelvic contain a piece of tissue about 4 × 3 × 1 cm in size and include five lymph nodes (Figure 1)

Microscopic examination showed that the tumor mass consisted of neoplastic cells forming a trabecular pattern, organoid, some with rosette formation, infiltrative between the connective tissue and a large area of necrosis. These cells conform to a uniform morphology. It showed a small, round-to-oval nucleus partially composed

of molding, narrow cytoplasm, chromatin salt and pepper, mitotic figure > 25/10 HPF (Figure 2A, B). Intravasal and perineural invasion were positive. At some other focus, neoplastic cells appear cribriform, solid, and tubular. These neoplastic cells showed a round to oval nuclei, hyperchromatism nuclei, increased N/C ratio, severe nuclear pleomorphism, eosinophilic cytoplasm, mitotic figure 5/10 HPF (Figure 2C, D). Right pelvic lymph nodes contain malignant cell metastases in all of the four lymph nodes. Left pelvic lymph nodes also contain malignant cell metastases in all of the five lymph nodes. Histopathologically, we concluded as a carcinoma, suspicious for Mixed Adeno-neuroendocrine Carcinoma (MANEC), malignant cell metastasis in all of the four right pelvic lymph nodes, and all of the five left pelvic lymph nodes. No visible malignant cell infiltration in the vaginal cuff, lower uterine segment, right and left parametrium, uterus, right fallopian tube, and left adnexa (pT1b pN1 pMx).

Immunohistochemistry examination using chromogranin-A showed a focal positive (patchy) cytoplasmic cell tumors. Synaptophysin is positively diffused on tumor cell cytoplasm, Ki-67 shows positive on malignant cell nuclei about > 90%, CEA shows focal positive on the cytoplasm of tumor cells (Figure 3A, B, C, D). This case was concluded as a high-grade Mixed Adeno-neuroendocrine carcinoma (MANEC).

DISCUSSION

Mixed Adenoneuroendocrine Carcinoma (MANEC) of the cervix is rare cancer with a poor prognosis. This type of malignancy accounts only for 1% of all malignancies of the cervix uteri. According to WHO classification, MANEC shows a combination of adenocarcinoma and neuroendocrine carcinoma, containing >30% of each component of the tumor cells.^{2,4,6,7} Clinically, a small cell neuroendocrine carcinoma is the most common tumor.¹ Very few studies report about MANEC, and most literature were small studies and case reports. Clinical features of small cell type neuroendocrine carcinoma have similarities with low-grade neuroendocrine tumors, namely the presence of vaginal bleeding and exophytic mass in the cervix with the median age of patients was 44 years (34-75 years).⁸ Similarly, vaginal bleeding occurs, which makes this patient seek medical attention, and the age was within the range mentioned in the previous literature. Additionally, an ultrasound examination revealed a cervical mass suspicious of malignancy.

It is worth to mention that suitable radiological examination is essential to help the clinical diagnosis and revealed the extend or size of the tumor

before surgery. FIGO approves the clinical examination that includes rectovaginal examination, chest radiograph, intravenous pyelogram, cystoscopy, and proctoscopy. However, rather than emphasizing clinical examinations and simple imaging, the physician in more advanced countries tend to opt for advanced radiological imaging studies such as computed tomography (CT) and magnetic resonance imaging (MRI).⁹

Histopathologically, small cell neuroendocrine carcinoma is characterized by a small population of monotonous/uniform cells which is generally resembling the small cell lung carcinoma. Small cell neuroendocrine carcinoma tends to produce diffuse growth, solid or non-cohesive, arranged molding, and little cytoplasm.² Usually, mitosis and apoptosis are numerous, and extensive necrosis often involves lymphovascular invasion (LVI). Recurrences are usually found at the extra pelvic region and bone, lymph node, supraclavicular, and lung. Small cell neuroendocrine carcinoma is an aggressive tumor. It is associated with high recurrence rates and distant metastases, even in its early stage.⁵

On the other hand, adenocarcinoma is an invasive epithelial tumor that shows glandular differentiation with atypical cells, hyperchromatic nucleus, and pleomorphism. Also, the presence of the mitotic figure and infiltration to the cervical stroma further strengthen the finding.¹⁰ Adenocarcinoma accounts for about 20% of all cervical cancers. Although cervical screening programs are beneficial in reducing the incidence of invasive squamous cell carcinoma of the cervix, it is relatively less successful in detecting adenocarcinoma precursor lesions. In general, 94% cervical adenocarcinoma is associated with Human Papillomavirus (HPV) infection, most commonly types 18, 16, and 45. Clinical manifestation of adenocarcinoma also involves abnormal uterine bleeding and mass in the cervix. Macroscopically tumors show an exophytic growth pattern in approximately 50% of cases.³

Cervical small-cell neuroendocrine carcinoma combined with adenocarcinoma, must consist of neuroendocrine components and non-neuroendocrine components that are well represented. These components may be completely separate but more often found mixed, which may not be easily seen. This primarily occurs in the case of neuroendocrine in combination with a poorly differentiated non-neuroendocrine component.⁵ In this patient, the neuroendocrine component and adenocarcinoma were found to be mixed.

Markers used for immunohistochemical detection of neuroendocrine differentiation of small cell cases were chromogranin (CgA), synaptophysin (Syn), and cell proliferation index (Ki-67).¹¹⁻¹³

Research on chromogranin is mostly done in neuroendocrine tumors. A previous study by Gut et al. (2016) stated in his research, chromogranin A (CgA) is a glycoprotein acid, member of the granin family that contains exclusively on dense core granules and is used as a storage place for peptide and catecholamine hormones in endocrine organs and neuroendocrine cells. Chromogranin A is a valuable tumor marker, although it has its limitations. Chromogranin expression is related to secretory vesicles present in neuroendocrine cells. Increased levels of CgA in neuroendocrine tumors due to increased secretion activity and CgA can increase significantly in tumor cells that have metastasized compared to tumor cells that are still limited on the original site. Tumor cells in patients with liver metastases are associated with significantly higher CgA concentration compared to cells that metastasize to lymph nodes. The sensitivity and specificity of CgA in those cases were estimated at around 60-100%.¹¹ In this patient, the CgA examination showed a focal (patchy) appearance in the cytoplasm of tumor cells.

In an earlier study found that synaptophysin is a glycoprotein that is expressed in neurosecretory cell membranes and is the most specific tumor marker. Synaptophysin can be detected in endocrine cells and in small synaptic membrane vesicles. Synaptophysin is an integral part of the major glycoprotein of neuronal synaptic vesicles and showed a high degree of development in humans.¹¹ In this study, synaptophysin was shown to be positively diffused in the cytoplasm of tumor cells.

Several other studies state that Ki-67 is a marker of cell proliferation, which is related to histopathological parameters and tumor grading.¹¹ In this patient, Ki-67 showed positive in >90% malignant cell nuclei. According to WHO the tumor was grading based on the percentage of Ki-67 and the number of mitoses, namely: grade 1 (G1) if Ki-67 \leq 2% and mitosis <2, grade 2 (G2) if Ki-67 3-20% and mitosis 2- 20, grade 3 (G3) if Ki-67 > 20% and mitosis > 20. Based on Ki-67 and number of mitosis, the tumor divided into NET (grade 1 and 2) and NEC (grade 3) high grade.^{5,10}

CONCLUSION

Mixed Adenoneuroendocrine Carcinoma (MANEC) is a combination of neuroendocrine components and non-neuroendocrine components, where each of these contributes >30% of the tumor cells. This rare case is aggressive, often involving lymph nodes and blood vessels, and is associated with high recurrence rates and distant metastases even in its initial stage. Clinically, this disease presented with vaginal

bleeding, painless mass in the cervix detected during an ultrasound examination, and an abnormal pap smear. The age at diagnosis is between 34 to 75 years, with a median age of 44 years old. The adenocarcinoma and neuroendocrine carcinoma component can be found separately or mixed, which makes it difficult to diagnose in the routine histopathological examination, so immunohistochemical examination for chromogranin A (CgA), synaptophysin (Syn), Ki-67 and CEA are essential. Based on clinical, radiological, histopathological, and immunohistochemical examinations, this case was concluded as MANEC.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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