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Case Report

Combined Carcinoid Carcinoma and Squamous Cell Carcinoma of the Endometrium: A Case Report and Survey of Related Literature

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Keywords
Neuroendocrine tumor · Hypothermia · Squamous cell carcinoma

Abstract
Introduction: Histologically, endometrial neuroendocrine carcinoma is an extremely rare pathological type of endometrial cancer. In addition, this type is characterized by high invasiveness and poor clinical outcome, which was classified into carcinoid (low grade), and small-cell and large-cell neuroendocrine carcinoma (high grade). Globally, reports on endometrial carcinoid carcinoma are limited. Clinically, it is also rare to see primary squamous cell carcinoma of endometrium. ***Case Presentation:*** Here, we report an interesting case of mixed carcinoma of endometrium with both carcinoid and squamous cell carcinoma, which presented with persistent vaginal bleeding and hyponatremia. ***Conclusion:*** Careful pathologic review is necessary to diagnose this rare disease. More studies in the future are warranted to demonstrate the primary surgical treatments and the efficacy of adjuvant therapy of this disease.

Introduction

Endometrial neuroendocrine carcinoma is a rare histological type, which presents with high invasiveness and poor prognosis. Patients diagnosed at advanced stage for most cases with no specific clinical symptoms. The most common symptom was vaginal bleeding, while a few patients seek medical help for paraneoplastic syndrome. Patients are diagnosed definitely with neuroendocrine carcinoma of the endometrium by pathology [1].

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Based on the classification criteria of WHO 2020, endometrial neuroendocrine carcinoma, similar to the gastrointestinal neuroendocrine carcinoma, is classified into low-grade and high-grade neuroendocrine carcinoma [2]. Primary carcinoid carcinoma is rare in gynecology oncology which presents most in the appendix [3]. And squamous cell carcinoma of endometrium is of low incidence. It is extremely rare to see the mixed carcinoid and squamous cell carcinoma of the endometrium. Here, we reported a 50-year-old female patient with a diagnosis of combined carcinoid carcinoma and squamous cell carcinoma of the endometrium, who presented with persistent vaginal bleeding and hyponatremia as the first symptom. This report is the first report on combined carcinoid carcinoma and squamous cell carcinoma of the endometrium, which is likely to provide reference for clinical treatments and diagnosis of this disease. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534622).

Case Report

A 50-year-old female patient with the main complaint of "irregular vaginal bleeding and fatigue for 6 months" visited our hospital on 12 February 2019. A mass was presented in the endometrium of the patient detected by ultrasonic examination. On pelvic MRI, a mass in the uterus involved deep muscular layer was confirmed as a 5*6 cm mass that appeared to be pelvic lymph node metastasis (Figure 1). Blood test showed a serous hyponatremia with Na^+ level of 123~131 mmol/L.

The patient received diagnostic curettage, and the pathological result showed high-grade malignant endometrial carcinoma. Tumor markers including carbohydrate antigens 125 (CA125) and human epididymis protein 4 were detected in normal ranges, and no intraepithelial or malignant lesions were found in cervical exfoliative cytology examination.

The uterus with enlargement in smooth and hard nature was found in the posterior position according to the gynecological examination. Hard nodules with poor activity and no tenderness can be touched in the anterior uterine wall. Based on the pathological result, endometrial carcinoma invading the serosa was diagnosed in the patient. For the huge mass in the endometrium and the poor state of patient, she received two circles of neoadjuvant chemotherapy with taxol and carboplatin, while improving the persistent hyponatremia, then staging operation of endometrial cancer was conducted under general anesthesia on 21 May 2019.

During the operation, it was found that the enlarged uterus was located in the middle of the pelvis, the size was about 60 days of pregnancy, and the surface was smooth. The appearance of the main ligament and bilateral fallopian tubes and ovaries was normal, and no tumor was found on the surface of the appendix, omenta, and peritonea. The lymph nodes in the pelvis and surrounding the abdominal aorta were enlarged. First, we get the cytology of peritoneal fluid which resulted negative. And then laparotomy radical hysterectomy with bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy was performed. Incision of the uterus showed that the solid tumor of the posterior wall of the uterus with diameter of 2 cm, slightly brittle texture and pale in color protruded from the muscle wall to the uterine cavity. No lesion was found in the vaginal fornix and cervix. The normal appearance of the bilateral attachments was found, and the lymph nodes in the pelvis and surrounding the abdominal aorta were evidently enlarged.

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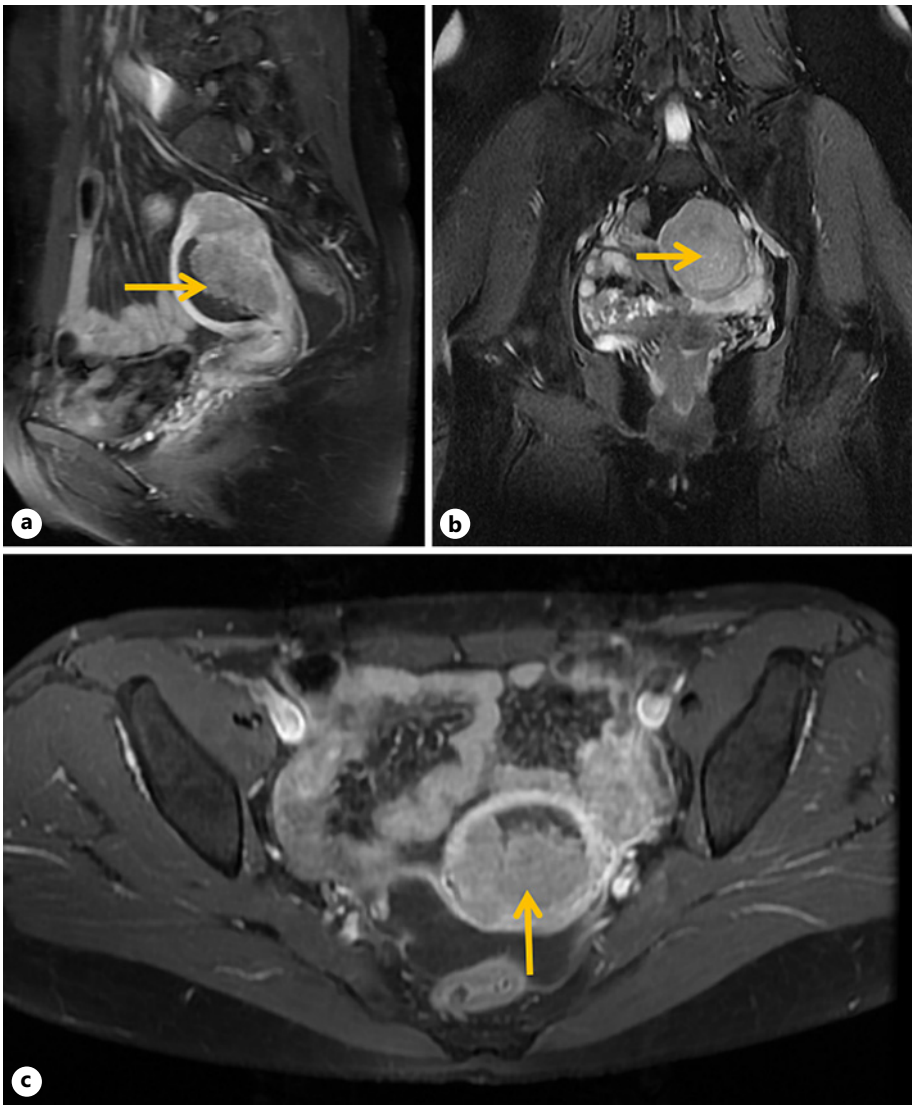

Fig. 1. a MRI. **b** Sagittal section. **c** Coronal section. Cross section shows an endometrial mass.

Pathological gross examination of the tumor showed that there was no obvious tumor in the serous surface membrane of the uterus. Incision of the uterus showed that the solid tumor of the posterior wall of the uterus with diameter of 2 cm, slightly brittle texture and pale in color protruded from the muscle wall to the uterine cavity. Microscopically, the endometrium was presented with mixed carcinoma. Histologically, two kinds of carcinoma were distributed separately. And the carcinoid was distributed in the muscles of myometrium with invasive pattern, accounting for about 70% of the tumor. Diffused infiltrating carcinoma of myometrium of the uterus is neuroendocrine tumor, with no obvious cellular atypia, abundant cytoplasm, rare mitograms of 0–1/10 HPF, Ki67 index of about 2%, consistent with carcinoid, multifocal vascular and lymphatic invasion, nerve invasion. Squamous cell carcinoma is arranged in the uterine body cavity, accounting for about 30% of the tumor (Figure 2). There is no glandular (or tubular) structure or keratinization of the tumor cell components. The tumor has penetrated the uterine serous membrane. Multi-lesions of lymphatic vessel space infiltration were found. Of the 23 harvested lymph nodes from the pelvic, 5 metastasized lymph nodes were identified in the abdominal aortic and left pelvic lymph nodes with mixed

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carcinoma. Negative reaction was displayed in the cervix, bilateral ovary, and oviduct. Immunohistochemically, in carcinoid carcinoma, the tumor cells were partly positive for synaptophysin (Syn), S-100, NSE, chromogranin A (CgA), CD56, cytokeratin (CK), H-CK, P63, and P40. The progesterone receptor and the estrogen receptor were negative. CA125, P16, Napsin A, WT-1, CD99, and vimentin were negative. The Ki67 proliferation index was 10%. Elastic fibers show vascular invasion. D2–40 showed lymph node metastasis. In squamous cell carcinoma, the tumor cells were partly positive for CK, CK7, CEA, P63, P40, PAx-8, and CEA. Additionally, results of villin, CDX-2, and CK20 were all negative. The histologic features of the tumor and its immunohistochemical profile support the diagnosis of carcinoid of the endometrium with squamous cell carcinoma (Fig. 2).

Based on the revision of FIGO 2009 staging for endometrial carcinoma, the patient was classified as stage IIIC2. Postoperatively, the patient was given adjuvant chemotherapy with cisplatin and etoposide under interval of 3 weeks and received "sandwich" therapy of chemotherapy-radiotherapy-chemotherapy. In the first circle of chemotherapy, grade 1 nausea and vomiting and grade 3 myelosuppression were developed in the patient. The patient received radiotherapy followed by 3 circles of chemotherapy with no sign of further deterioration. A complete response was achieved in the patient on the basis of the RECIST1.1 criteria. She is currently under close follow-up with no recurrence for 4 years and 4 months after surgery.

Discussion

Neuroendocrine carcinoma (NEC) is classified into low-grade and high-grade. High-grade NEC included small-cell carcinoma and large-cell neuroendocrine carcinoma, while low-grade NEC included typical and atypical carcinoids [4]. Carcinoid carcinoma is a rare histological type of low-grade neuroendocrine carcinoma [5]. Carcinoid carcinoma of the endometrium is also very rare to see in clinic [6]. According to the database of Surveillance, Epidemiology, and End Result (SEER) program, there were only 2 cases of endometrial carcinoid carcinoma reported in America from 1975 to 2016. In fact, simple carcinoid carcinoma is not common to see, as well as mixed with other type of pathology such as adenocarcinoma. In our case, carcinoid carcinoma (accounting for 70%) combined with squamous cell carcinoma (accounting for 30%) is presented.

Of gynecological neuroendocrine carcinomas, the small-cell carcinoma of the cervix which typically behaves aggressively is the most common to see. Ovarian carcinoid carcinoma usually with benign behaviors and organ limitation was reported sometimes. The clinical features of gynecological neuroendocrine carcinomas are nonspecific and always depend on the origin of organs and the extent and invasiveness of the disease [7].

The average age of patients with endometrial carcinoma is reportedly about 60 years, and 75% of these patients occur over 50 years. More than 90% of patients with endometrioid carcinoma, especially those after menopause, presented with vaginal bleeding [8]. According to the literature, the diagnosed age of NEC ranges from 38 to 85 years, and the median age at diagnosis is 57 years [9]. The most common clinical manifestation of NEC of endometrium is abnormal vaginal bleeding, and this patient presented with persistent hyponatremia in addition to vaginal bleeding, which is paraneoplastic syndrome. About 70% of patients with endometrial carcinoma are confined to the uterus with negative pelvic examination and no significant uterine enlargement [8]. Staging is a key factor for the prognosis of endometrial carcinoma. However, it is not an effective factor for prognosis of NEC of endometrium due to the limited data of patients and the advanced stages at diagnosis of the disease [10]. In this case, the patient was diagnosed at stage IIIC2.

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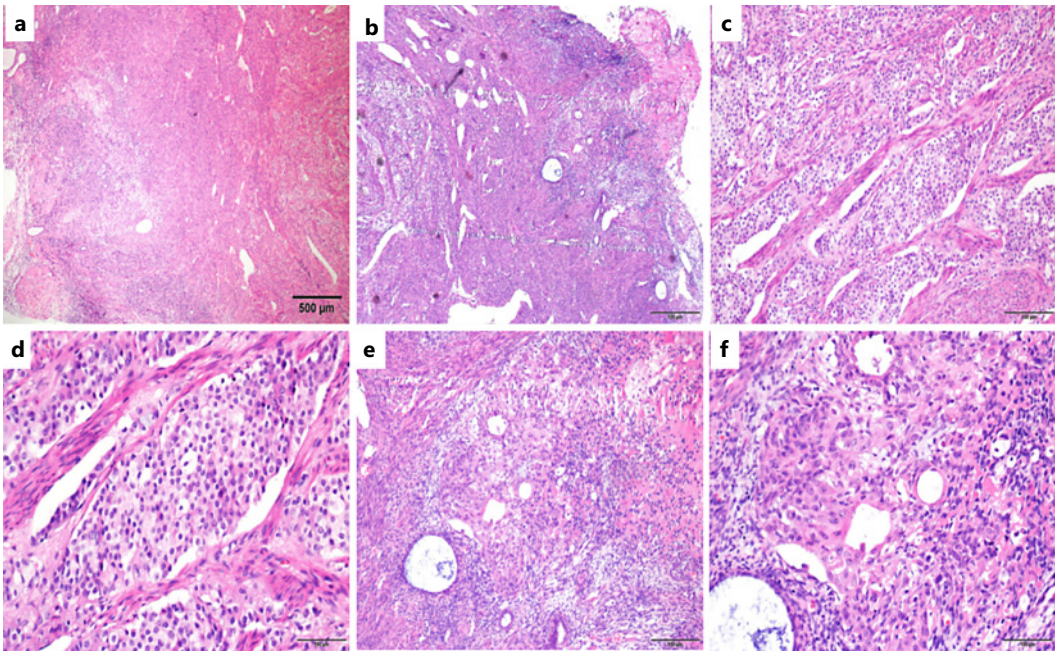

Fig. 2. Histological findings of endometrium: mixed carcinoma of carcinoid and squamous cell carcinoma (**a**, **b**); carcinoid carcinoma: neoplastic cells were uniform with small round nuclei, without atypia or mitotic activity (hematoxylin and eosin, scale bar 100 μm) (**c**, **d**); squamous cell carcinoma (hematoxylin and eosin, scale bar 100 μm) (**e**, **f**).

According to clinical pathology, key diagnosed factors of NEC were immunohistochemical examination [11]. In this case report, patients were presented with carcinoid with squamous carcinoma, and the immunohistochemistry demonstrated markers: in carcinoid carcinoma, the tumor cells were partly positive for synaptophysin (Syn), S-100, NSE, chromogranin A (CgA), CD56, cytokeratin (CK), H-CK, P63, and P40. The progesterone receptor and the estrogen receptor were negative. CA125, P16, Napsin A, WT-1, CD99, and vimentin were negative. The Ki67 proliferation index was 10%. Elastic fibers show vascular invasion. D2–40 showed lymph node metastasis. In squamous cell carcinoma, the tumor cells were partly positive for CK, CK7, CEA, P63, P40, PAx-8, and CEA. Additionally, results of villin, CDX-2, and CK20 were all negative.

No standard treatment guideline was existed for endometrial carcinoid carcinoma due to its rarity, and the traditional treatments such as surgical resection, radiation therapy, and chemotherapy of endometrial and other neuroendocrine tumors like small-cell lung cancer provide the reference to the treatment of endometrial carcinoid carcinoma [12]. The hysterectomy and bilateral salpingo-oophorectomy with lymph node assessment are the main treatments for endometrial carcinoma, and postoperative adjuvant therapy is performed for prevention of tumor recurrence considering the risk factors. Radiotherapy and chemotherapy are the most common adjuvant treatment. In recent years, the application of targeted therapy and immunotherapy in endometrial carcinoma is increasing, especially in advanced disease. The exploration of immune checkpoint inhibitors in neuroendocrine tumors shows that it can be considered for some selective populations. PD-L1, TMB-H, and MSI-H/dMMR are all biomarkers associated with immunotherapy effect. In our study, the patient was given the treatments above with postoperative "sandwich" treatment of chemo-radio-chemotherapy expecting to achieve optimal disease control.

Conclusion

Patients with primary carcinoid and squamous cell carcinoma of the endometrium are rare to see. Careful pathologic review of the hysterectomy specimen is necessary to diagnose this rare disease. The underlying etiology of this condition has not been determined. More studies in the future are warranted to demonstrate the primary surgical treatments and the efficacy of adjuvant therapy of this disease.

Statement of Ethics

The present research was approved by the Ethical Committee and Institutional Review Board of Beijing Chao-Yang Hospital, Capital Medical University (2016-Scientific-166). We declare that written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Funding Sources

No funding was received.

Author Contributions

Ying Han and CuiQin Sang designed the study and managed the patient data. Ying Han was a major contributor in writing the manuscript. YanJun Zhang and Lin Niu offered the pathology and radiology data, respectively. All authors read and approved the final manuscript.

Data Availability Statement

Data are available on request due to privacy/ethical restrictions. Further inquiries can be directed to the corresponding author.

References

1 Chun YK. Neuroendocrine tumors of the female reproductive tract: a literature review. J Pathol Transl Med. 2015;49(6):450–61.
2 Matsumoto H, Shimokawa M, Nasu K, Shikama A, Shiozaki T, Futagami M, et al. Clinicopathologic features, treatment, prognosis and prognostic factors of neuroendocrine carcinoma of the endometrium: a retrospective analysis of 42 cases from the Kansai Clinical Oncology Group/Intergroup study in Japan. J Gynecol Oncol. 2019;30(6):e103.
3 Howitt BE, Kelly P, McCluggage WG. Pathology of neuroendocrine tumours of the female genital tract. Curr Oncol Rep. 2017;19(9):59.

4 Hu R, Jiang J, Song G, Zhu C, Chen L, Wang C, et al. Mixed large and small cell neuroendocrine carcinoma of the endometrium with serous carcinoma: a case report and literature review. Medicine. 2019;98(29):e16433.
5 Lopes Dias J, Cunha TM, Gomes FV, Callé C, Félix A. Neuroendocrine tumours of the female genital tract: a case-based imaging review with pathological correlation. Insights Imaging. 2015;6(1):43–52.
6 Pan Z, Repertinger S, Leonard R, Bewtra C, Gatalica Z, Sharma P. Cervical and endometrial metastases of appendiceal goblet cell carcinoid. Arch Pathol Lab Med. 2010;134(5):776–80.
7 Zegarac M, Nikolic S, Kolarevic D, Kocic M, Djurisic I, Inic Z, et al. Goblet cell carcinoid of the appendix. Review of the literature a propos of a rare case of endometrial metastases. J BUON. 2018;23(4):867–71.
8 Raffone A, Seracchioli R, Raimondo D, Maletta M, Travaglino A, Raimondo I, et al. Prevalence of adenomyosis in endometrial cancer patients: a systematic review and meta-analysis. Arch Gynecol Obstet. 2021;303(1):47–53.
9 Akgor U, Kuru O, Sakinci M, Boyraz G, Sen S, Cakir I, et al. Neuroendocrine carcinoma of the endometrium: a very rare gynecologic malignancy. J Gynecol Obstet Hum Reprod. 2021;50(5):101897.
10 Pocrnich CE, Ramalingam P, Euscher ED, Malpica A. Neuroendocrine carcinoma of the endometrium: a clinicopathologic study of 25 cases. Am J Surg Pathol. 2016;40(5):577–86.
11 Kawashima I, Fukasawa H, Kasai K, Kumagai T, Koshiishi M, Nakajima K, et al. Bone marrow invasion of small cell neuroendocrine carcinoma of the endometrium: a diagnostic pitfall mimicking a haematological malignancy. Intern Med. 2019;58(17):2561–8.
12 Lee YM, Yeo MK, Choi SY, Kim KH, Suh KS. Peritoneal fluid cytology of disseminated large cell neuroendocrine carcinoma combined with endometrioid adenocarcinoma of the endometrium. J Pathol Transl Med. 2019;53(6):407–10.