Case Report

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Small cell carcinoma of the cervix complicated by syndrome of inappropriate antidiuretic hormone secretion: a case report

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Abstract

Small cell carcinoma of the cervix is a rare malignant tumor in the clinical setting. Clinical manifestations of this tumor are mostly similar to those of normal types of cervical cancer. Small cell carcinoma of the cervix only shows symptoms of neuroendocrine tumors, such as syndrome of inappropriate antidiuretic hormone secretion (SIADH). Most of the hyponatremia caused by SIADH can be managed after removal of the cause. Hyponatremia is a predictor of poor prognosis and can be used as an indicator of partial recurrence. We report a case of small cell carcinoma of the cervix complicated by SIADH. Our patient presented with irregular vaginal bleeding after menopause. After one cycle of chemotherapy, there was trembling of the limbs, and a laboratory examination showed low Na^+ and low Cl^- levels. After limited water intake, intravenous hypertonic saline, and intermittent diuretic treatment, the patient's blood Na^+ levels returned to normal. After a radical operation, the above-mentioned symptoms disappeared.

Keywords

Small cell carcinoma of the cervix, syndrome of inappropriate antidiuretic hormone secretion, hyponatremia, neuroendocrine tumor, chemotherapy, electrolyte

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Background

Small cell carcinoma of the cervix (SCCC), which is also known as small cell neuroendocrine carcinoma of the cervix, is a rare

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neuroendocrine tumor with unique biological behavior. Immunohistochemistry has shown the neuroendocrine characteristics of some SCCCs, but most of their clinical manifestations are similar to common types of cervical malignancies. Furthermore, only a few patients with SCCC present with symptoms of a neuroendocrine tumor,[1] such as Cushing's syndrome and the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The present study describes a case of SCCC complicated by SIADH in our hospital.

Case presentation

General information

A 55-year-old female patient presented to our hospital in April 2018 owing to irregular vaginal bleeding for longer than 1 month after menopause. There was no contact bleeding or abnormal vaginal discharge. Gynecological ultrasound showed a $5.13 \times 4.51 \times 4.71$-cm hypoechoic area below the uterus with a rough and "moth-eaten" margin (cervical cancer was suspected). A ThinPrep cytological test was negative and human papilloma virus was 18(+).Colposcopy showed a thick waxy-like substance on the surface of the cervix and an extremely vascular appearance. Pathological findings on cervical biopsy showed SCCC. The immunohistochemical profile showed positivity for a neural cell adhesion molecule (CD56), chromogranin (focal+), Ki-67 staining (+40%), and positivity for synaptophysin.

A vaginal examination showed cervical swelling of approximately 5 cm in diameter, with an uneven surface, a visible biopsy scar, and contact bleeding. Bilateral parametrial pelvic tissue was not thickened and bilateral uterosacral ligaments were elastic.

Diagnosis and treatment process

Computed tomography showed a high volume of the cervix and a nodule shadow with a size of $4.8 \times 5.7 \times 6.2\,cm^3$. The nodule shadow showed uneven enhancement, and an unclear boundary between the local cervix and posterior wall of the bladder (Figure 1a). The blood Na^+ level was 139.5 mmol/L (normal range: 137–147 mmol/L) and the blood Cl^- level was 97.5 mmol/L (normal range: 99–110 mmol/L). Because of the large volume of the

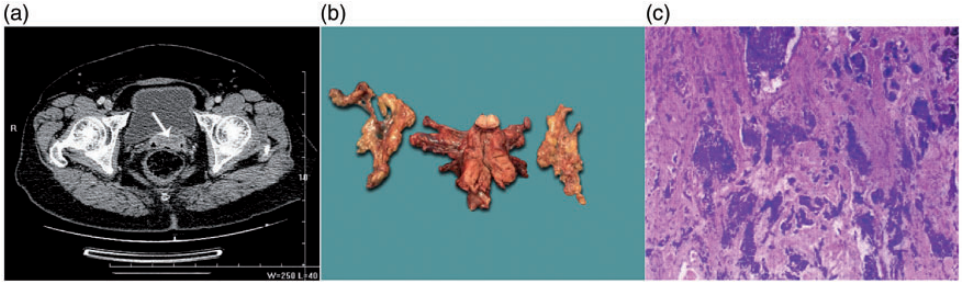

Figure 1. Contrast-enhanced computed tomography of the pelvis (a). The arrow indicates a cervical lesion, which is approximately $4.8 \times 5.7 \times 6.2$ cm^3 in size. The lesion shows uneven enhancement, and an unclear boundary between the local cervix and posterior wall of the bladder. Dissected specimen postoperatively (b). Cervical swelling of approximately 5 cm in diameter can be seen. Additionally, there was a hard endogenous mass in the cervical canal, which was located in the posterior wall of the cervix, and an enlarged lymph node with a diameter of approximately 1 cm in the right inguinal region. Image showing pathology under a light microscope (c) (hematoxylin and eosin, × 100). Cervical cancer cells and tumor thrombus were found in the vasculature.

lesion, neoadjuvant chemotherapy with paclitaxel liposome + lobaplatin injection was performed on 26 April 2018.

The patient was readmitted to our hospital at 1 month after chemotherapy. A laboratory examination showed a blood Na^+ level of 135.4 mmol/L and Cl^- level of 95 mmol/L, but no abnormalities were observed in the remaining tests. A vaginal examination showed no considerable change in the size of the cervix. Surgery was planned, and after bowel preparation, the patient suddenly suffered from trembling of the limbs, especially the upper limbs. This was accompanied by mild nausea and vomiting, without abdominal distension or a change in consciousness. An electrolyte test showed a Na^+ level of 123.2 mmol/L, Cl^- level of 82.5 mmol/L, and K^+ level of 3.69 mmol/L. After supplementing with hypertonic saline, the patient's blood Na^+ levels fluctuated between 121.0 and 129.1 mmol/L, and blood Cl^- levels fluctuated between 82.5 and 91.1 mmol/L, which suggested no improvement. After consultation with endocrine specialists, tests showed the following results: a urine Na^+ level of 540.3 mmol/24 hours (normal range: 130–260 mmol/24 hours), urine Cl^- level of 585.6 mmol/24 hours (normal range: 170–250 mmol/24 hours), urine osmotic pressure of 430.0 mOsm/(kg·H_2O), and plasma osmotic pressure of 274.0 mOsm/(kg·H_2O). SIADH caused by SCCC was highly suspected. Blood Na^+ levels returned to the normal range after treatment with limited water intake, intravenous hypertonic saline, and intermittent diuretic therapy. On 8 June 2018, extensive hysterectomy + bilateral adnexectomy + pelvic lymphadenectomy were performed. Intraoperative gross examination of the specimen showed cervical swelling of approximately 5 cm in diameter and a hard endogenous mass in the cervical canal, which was located in the posterior wall of the cervix. Additionally, an enlarged lymph node with a diameter of approximately 1 cm in the right inguinal region was observed. Blood Na^+ levels were monitored after surgery. Postoperative pathology confirmed the diagnosis of SCCC. The size of the tumor was approximately $3 \times 3 \times 2$ cm. The tumor invaded the whole wall of the cervix and an intraductal tumor thrombus was present (Figure 1b). The tumor was detected in the endocervical canal and in the left parametrium, but the remaining tissues were not involved. Lymph node metastasis was observed in the left and right pelvic areas (1/8 and 1/16).

After two chemotherapy sessions of paclitaxel liposome + lobaplatin injection, the patient was transferred for concurrent chemoradiotherapy. The static intensity adjustment technique was used and the target areas of postoperative radiotherapy were as follows: the vaginal stump, including fat and soft tissue between the bladder and rectum and the interrectal vaginal stump; paravaginal/parauterine tissue and the proximal vagina (including the vaginal stump); and total iliac, internal iliac, and external iliac lymphatic drainage and the anterior sacral region. The dose of radiotherapy was 50 Gy/25 times, 2 Gy/day, five times a week.

After completion of the radiotherapy and chemotherapy, the patient was followed up for 48 months. To date, there have been no signs of recurrence.

Discussion

SCCC of the female genital tract is rare in the clinical setting, and it is most commonly found in the cervix, followed by the ovary and endometrium.[2–9] Because of the unique biological behavior of SCCC, lymph node and vascular invasion are likely, even after early diagnosis. The SCCC recurrence rate is high, it is prone to early distant metastasis, and the probability of distant metastasis is significantly higher than that of common

cervical squamous cell carcinoma.[10] Our patient's pathology suggested vascular and lymph node metastasis, which is consistent with previous studies.[10] Diagnosis of SCCC depends on histomorphology, and a combination of histomorphology with immunohistochemistry can improve its diagnostic rate. The morphology of SCCC under a light microscope is similar to that of small lung cell carcinoma. SCCC is characterized by small round cells with the same shape and size, a reduced cytoplasm, deep nuclear staining, a reduced amount of mitotic images, a reduced amount of nucleoli, and fine granular chromatin. Most cancer cells grow diffusely and are often accompanied by necrosis (Figure 1c). SCCC is divided into simple and mixed types. The mixed type is often accompanied by squamous cell carcinoma or adenocarcinoma, but the proportion of small cells is uncertain. Commonly used immunohistochemical markers for SCCC include chromogranin, synaptophysin, CD56, and neuronal specific enolase. A retrospective study[9] showed that 31.25% of cases of SCCC showed positivity to thyroid transcription factor 1 and 50% were positive for caudal-related homeobox 2. However, expression rates of thyroid transcription factor 1 and caudal-related homeobox 2 cannot be used to distinguish a cervical endocrine tumor as primary or metastasis. These expression rates can be combined with the clinical history, such as the first symptom(s), regardless of whether there is a cervical precancerous lesion.

SCCC is often confused with the following diseases. (1) Undifferentiated carcinoma of the endometrium in the lower segment of the uterus is often characterized by irregular vaginal bleeding, and it can be characterized by positive markers of neuroendocrine carcinoma. Therefore, we need to further rely on segmented curettage and magnetic resonance imaging to distinguish the location of lesions. (2) In metastatic cancer, pulmonary and extra-pulmonary neuroendocrine cancers metastasize to the cervix, and other areas are often metastatic. Only transfer to the cervix is rare. Therefore, the clinical history needs to be combined with initial symptoms, combined symptoms, and imaging techniques, such as positron emission tomography-computed tomography, to distinguish the initial site of SCCC. (3) Small cell non-keratinized squamous cell carcinoma of the cervix shows microscopic small oval basal-like cells with a lamellar or nested distribution, there is rarely a cytoplasm, there is deep nuclear staining, and mitosis is common. However, immunohistochemical neuroendocrine markers are negative. (4) Primary cervical lymphoma is rare, with an incidence of $<1\%$, and its identification depends on light microscopy. Under a microscope, heterogeneous lymphocytes can be seen with a loose arrangement. This lymphoma infiltrates the cervical stroma, without destroying the glandular structure, and vascular wall infiltration is characteristic. Immunohistochemistry shows positivity for CD45 and neuroendocrine markers are negative. (5) Embryonic rhabdomyosarcoma, also known as grape-like sarcoma, is rare in clinical practice. This condition is positive for muscle markers, including myosin and myogenin, and negative for neuroendocrine markers.

SIADH refers to a group of syndromes that are characterized by excessive release of endogenous antidiuretic hormone (also called arginine vasopressin) or excessive activity. This results in various clinical manifestations, such as water retention, increased urinary sodium excretion, and volumetric hyponatremia. SIADH is the most common cause of hyponatremia in the clinical setting,[11] SIADH usually occurs in small cell lung cancer, and approximately 15% of patients with small cell lung cancer suffer from SIADH.[12,13] Numerous studies have shown that SCCC

complicated by hyponatremia predicts a poor prognosis.[14] A study conducted by Tai et al.[15] showed that among 244 cases of small cell lung cancer, approximately 70% of SIADH cases had recurrence with recurrence of the tumor. Han and Kong reached the same conclusion that most SIADH cases recur with recurrence of the tumor in SCCC.[16] Therefore, for high-risk patients, physicians should pay special attention to changes in electrolytes.

Conclusion

SCCC is an endocrine tumor that is rare and extremely malignant in clinical practice. SCCC complicated by SIADH is even less common, and most of these patients recover quickly after removal of the causes. Combined hyponatremia often indicates a poor prognosis. Therefore, hyponatremia may be used as an indicator of recurrence. Hyponatremia deserves attention in clinical practice, and is beneficial for early diagnosis and treatment, thereby improving the prognosis of SCCC complicated by SIADH.

Ethics statement

Written informed consent for publication was obtained from the patient. The present study was approved by the Ethics Committee of the Second Hospital of Hebei Medical University (2020-P051).

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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