

Small cell neuroendocrine carcinoma of the endometrium, a rare aggressive tumor

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ABSTRACT

This is a report of a young infertile woman with a history of 8 years amenorrhea, who presented with history of vaginal bleeding of 2 months duration. Investigations revealed a small cell neuroendocrine carcinoma of the endometrium, which penetrated half of the thickness of uterine wall. We have described the clinical progress and management of this rare and highly malignant cancer. A review of the pathological types and behavior of clear cell neuroendocrine carcinoma is presented.

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Small cell neuroendocrine (NE) carcinomas of the genital tract are very rare tumors. Most often poorly differentiated and highly aggressive.¹ They include 4 categories: carcinoid tumor; small cell carcinoma; large cell neuroendocrine carcinoma; and small cell carcinoma with focal large cell of NE carcinoma.² Heterogeneity in this group of tumors has been known to be the rule rather than the exception. They are frequently associated with squamous or glandular differentiation. Patient may develop early metastasis.

Imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) are used for staging of these tumors. Magnetic resonance imaging is the best modality due to its multiplanar capabilities. Treatment includes radiotherapy, chemotherapy and surgical resection. Recent clinical research suggests that unlike poorly differentiated NE carcinomas of various sites, small cell NE carcinoma is mostly nonsensitive to chemotherapy in advanced stages. Aggressive initial multimodality treatment is recommended, since relapses cannot be salvaged.³

We present a case report of a young woman with a history of primary ovarian failure, which terminated into heavy and prolonged vaginal bleeding. Investigation revealed NE carcinoma. Her management and follow-up will be described.

Case Report. A 31-year-old divorced and obese, nulliparous Bahraini woman attended the gynecological out-patient clinic complaining of heavy and prolonged intermittent vaginal bleeding of 3 months duration. It was associated with lower abdominal cramps like pain. Prior to this, she had amenorrhea for 8 years and could only have withdrawal bleeding in response to cyclical hormone until the start of this episode of bleeding. She was once married for a period of 4 months but currently she is divorced. There was no history of hormone therapy or any other medications. No serious illnesses or operations and no significant family history elicited. Vital signs and general physical examination were normal. On pelvic examination, there were cervical necrotic tissues

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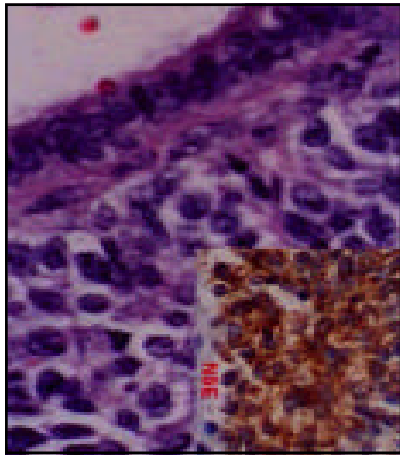


Figure 1 - Micrograph of tumor showing dark round cells in solid nests and trabecular pattern. (hematoxylin and eosin x 160). Inset-strong neuron specific enolase positivity in the tumor cells (Pap x 160).

with slight bleeding. The uterus was bulky and there was no adnexal lesion Pap smear could not be collected as she was having vaginal bleeding.

She was advised admission for hysteroscopy and fractional curettage (D&C). On admission, the hemoglobin level was found to be 6.9 g/dl, so she was transfused with 2 units of blood preoperatively. The following day, she had the hysteroscopy and D&C. A profuse and suspicious looking endometrium was obtained and sent for histopathological examination. The CT scan of the abdomen and pelvis revealed no evidence of infiltration into adjacent tissues and no evidence of local or adjacent metastasis. Normal findings was obtained through intravenous pyelography, however, extrinsic impression on the bladder was possibly due to bulky uterus. Pelvic ultrasound showed hypoechoic area in the anterior uterine wall suggestive of fibroid 2.7 by 1.6 cm. Tumor markers showed carcinoembryonic antigen of 1.9 u g /L and alpha fetoprotein 1.1 u g/L.

In the light of these findings, the patient and her next of kin were interviewed and informed regarding the nature of findings, the treatment options and the prognosis. They agreed that she should have a hysterectomy and any other surgical procedures that may be necessary. Preoperative workup included: hemoglobin 10.2 g/dl, packed cell volume 32%, white blood cell 24.6 $10^9/L$, urinalysis, blood gases, liver function tests, urea, blood sugar and electrolytes were normal.

She undergone total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy combined with cystoscopy and bilateral ureteric catheterization. The findings were: uterus enlarged to 14 weeks gestation size, both tubes and ovaries were normal. There were no pelvic adhesions or

metastasis, The liver diaphragm and omentum were normal. The postoperative period was generally uneventful apart from slight abdominal wound gapping, which was treated satisfactorily.

The histopathological examination of the endometrial biopsy revealed a cellular tumor composed of small round oval cells arranged in solid trabecular pattern with perivascular arrangement. (Figure 1) Individual cells showed hyperchromatic nuclei, fine chromatin, inconspicuous nucleoli and scanty cytoplasm around. Few endometrial glands were incarcerated by the tumor, which showed mild cellular pleomorphism and occasional mitosis. There was lack of squamoid or glandular differentiation. Also, no cartilage or skeletal muscle elements were found in the neoplasm. Hemorrhage and necrosis were present in foci. Immunohistochemistry revealed positive neuron specific enolase (NSE) CD20, while CD45 RO were negative.

Based on the light microscopic features, supported by strong NSE positivity, a diagnosis of NE carcinoma of endometrium was given.

The patient was seen by Oncologist who suggested that in the light of her histopathological findings and high recurrence rate, she should have postoperative radiotherapy. The external radiation treatment consisted of C 5040 cGY in 28 fraction given, using 4 field technique. This treatment was given over 6 weeks period. The patient was referred to King Faisal Specialist Hospital, Riyadh, Kingdom of Saudi Arabia where she received 2 sessions of high dose rate brachytherapy boost to the vaginal vault (500 cGY to 0.5 cm depth each session).

Four months after she completed her treatment, she was admitted to Salmaniya Medical Complex, with obstructive uropathy. Ultrasound showed bilateral hydronephrosis with renal pelvic dilatation. Unfortunately, she left the hospital against medical advice. In the following week, she was readmitted through accident and emergency with abdominal distension and edema. Investigations revealed renal failure with fluid overload. She was started on hemodialysis and had a nephrostomy.

Her CT scan revealed moderate amount of retroperitoneal lymphadenopathy encasing inferior vena cava and aorta was noted. It extended from the renal vein to the aortic bifurcation. A 7 cm cyst in upper left renal pole with subcapsular hematoma was seen. There was moderate bilateral hydronephrosis. The liver and the spleen were normal.

A cystoscopic bilateral double J stents was inserted, but this was not effective and the patient was discharged from hospital as terminal case with no further access to dialysis, but was given

supportive treatment. She was readmitted the following day and found to have Methicillin Resistant *Staphylococcus aureus* septicemia, which was treated with Vancomycin with no avail. She died 2 days later.

DISCUSSION. While small cell NE carcinomas NE can occur anywhere, it is encountered mainly in the respiratory system accounting for 20% of all lung cancer. In the genital tract, they are extremely rare and mostly poorly differentiated, chemoresistant and associated with a very poor prognosis. The mean age at the initial diagnosis is 35 years and most of the cases are advanced by the time they seek help. Neuroendocrine clear cell tumors can arise de novo from the ovary, endometrium or cervix and rarely in the vagina. Most of the uterine tumors are bulky, intraluminal and invade at least half of the myometrial thickness.¹⁻³

Clinically, NE carcinomas is associated with a number of paraneoplastic syndromes. The tumor cells may produce ectopic adrenocorticotrophic hormone, resulting in Cushing's syndrome. Another paraneoplastic hormone syndrome that commonly occurs is the syndrome of inappropriate antidiuretic hormone. This is caused by secretion of antidiuretic hormone from the tumor. Another paraneoplastic syndrome associated with small cell NE carcinoma is Eaton-Lambert syndrome, also known as myasthenic syndrome. It is characterized by fatigability, dry mouth and paresthesia. Unlike myasthenia, however, Eaton-Lambert is associated with improved strength with repeated muscle activity. Finally, small cell carcinoma is the most common cause of superior vena cava syndrome.

Pathological diagnosis of these tumors is usually achieved by undertaking immunohistochemistry on the paraffin section. These neoplasm show positivity for neuron specific enolase, chromogranin, cytokines and carcinoembryonic antigen. Presence of dense core neurosecretory granules on electron microscopic study further supports the diagnosis of NE carcinoma.⁴

Although few reports have suggested a better prognosis if patients are treated early, the majority die or have advanced metastasis within one year of diagnosis.⁵

In this case, the patient was young and childless and the prospect of undergoing hysterectomy was quite shocking, which can explain her initial reluctance to accept the treatment. Looking back, the surgery should have been more radical with

Wertheims' hysterectomy and lymphadenectomy as the preferred course, however, our experience with such an aggressive tumor is limited. In fact, this was the only case of neuroendocrine carcinoma of the genital tract, which we have encountered over the last 2 decades.⁶

The histopathological difficulty in differentiating between the NE carcinoma and homologous-type of stromal mesodermal mixed tumor is common and immunohistochemical evidence or even ultra structure microscopy in these situations may be necessary to confirm the diagnosis of NE carcinomas.⁷

Postoperative radiotherapy was started as soon as the patient was fit to receive it. She was given the full course in Salmaniya Medical Complex with the exception of the brachytherapy, which was carried out at the King Faisal Specialist Hospital in the Kingdom of Saudi Arabia. Her sudden deterioration after her returning to Bahrain was associated with uremia and secondary obstructive uropathy caused by metastasis.

In conclusion, small cell NE carcinoma of the uterus is a challenging and rare cancer, which requires early and accurate histopathological diagnosis, radical surgery and a combination of radio and chemotherapy.⁸

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