Small Cell Neuroendocrine Carcinoma of the Endometrium - A Rare but Aggressive Tumor: A Case Report

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Abstract

Small Cell Neuroendocrine Carcinoma (SCNEC) of the uterus is a rare tumor, very aggressive and highly invasive. SCNEC accounts for only 2% of genital tract tumors, and its rarity highlights the challenges faced in the management. It most commonly occurs in perimenopausal and postmenopausal women, is diagnosed at an advanced stage, and carries a poor outcome. Here, we describe a case of SCNEC of the endometrium in a 69-year-old lady. Cancer was stage III at the time of diagnosis. Tumor cells were positive for immunohistochemical stains CD56 and Synaptophysin. The patient was treated with surgery, chemotherapy, and radiotherapy, but she ultimately succumbed to infections four months after the diagnosis. Due to the rarity of SCNEC and unavailability of a unified treatment strategy, the data is still scarce, opening future research windows.

Keywords: *Female genital tract tumors, neuroendocrine carcinoma, small cell neuroendocrine carcinoma of the endometrium, neuroendocrine tumors, small cell carcinoma.*

INTRODUCTION

Small cell Neuroendocrine carcinoma (SCNEC) of the uterus is a rare, very aggressive, and highly invasive tumor. SCNEC most commonly occurs in perimenopausal and postmenopausal women and carries a poor outcome. This tumor is usually diagnosed at a high stage and has frequently metastasized by that time [1]. In the uterus, it more frequently arises from the cervix, endometrial SCNEC is rare and is commonly mixed with other tumors, such as Endometrioid carcinoma and Adenosquamous carcinoma [2].

We describe a case of SCNEC of the uterus in an elderly lady, diagnosed at stage III and treated with surgery, chemotherapy, and radiotherapy. Regrettably, the patient succumbed to infections four months after the diagnosis.

CASE REPORT

A 69-year-old female known case of Hypertension and Diabetes Mellitus (controlled on anti-hypertensives and oral hypoglycemic drugs), and addicted to betel leaf, P4+0 (previous all spontaneous vaginal deliveries, with last born 35 years ago) and menopausal since the age of 56 years, presented to the Gynecology clinic with the complaint of abdominal pain and distension for six months. These symptoms were gradually increasing in severity and were accompanied by constipation and esophageal reflux. She also had a complaint of early satiety; however, neither she nor her family noticed any weight gain or loss, and no prior data was available for comparison. Her family history was positive for cancers, one of the close relatives from the paternal side had an oral cancer and eventually died of it. On examination, a large irregular mass of approximately 15 x 15 cm was felt in her pelvis, with ill-defined margins reaching the umbilicus. CT scan showed a large heterogeneously enhancing mass lesion in the pelvis, measuring 16x15.9x10.5 cm (**Fig. 1**). The tumor showed low-density areas representing necrosis, was extending into the lower abdomen, and was inseparable anteriorly from the urinary bladder. Posteriorly. It was closely abutting the sigmoid colon. Both ovaries could not be separately visualized. These radiological findings were suggestive of a neoplastic lesion. The case was discussed in the tumor board meeting, and surgery was planned, taking the general surgeon, urologist, and urogynecologist on board, as the mass was suspected to be involving the sigmoid colon and the urinary bladder. The patient was operated on with general anesthesia, and debulking surgery was performed, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, and infrasonic omentectomy. However, intra-operatively, the colon and bladder were not found to be involved. Therefore, these were not resected. Ureteric stenting

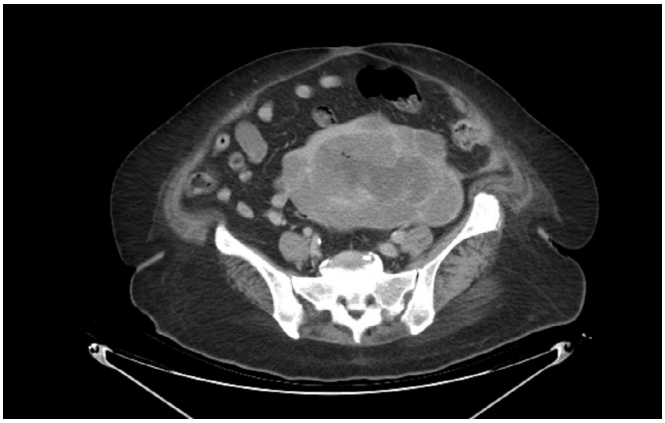

Fig. (1): CT scan, transverse section through pelvis showing tumor mass.

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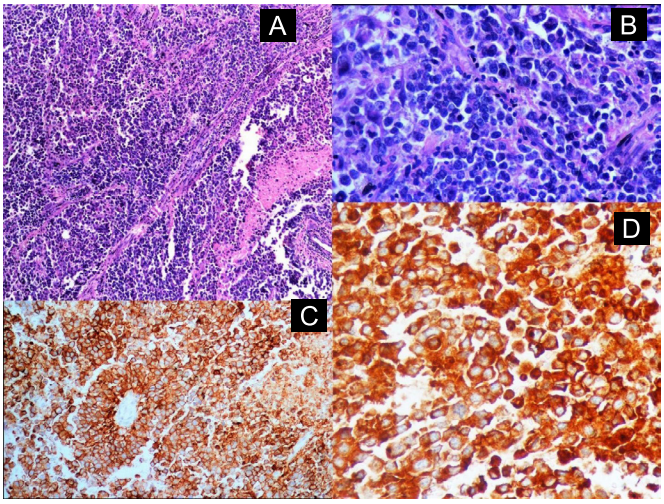

Fig. (2): **(A)** Small cell carcinoma, low power (10X), Hematoxylin and Eosin (H & E) stain. **(B)** High power magnification (40X), tumor cells show hyperchromatic nuclei. **(C)** Immunohistochemical stain Synaptophysin, tumor cells are positive. **(D)** CD56 stain, tumor cells are strongly positive

was performed before surgery, and stents were removed before the discharge of the patient. The specimen was sent for Histopathology.

On gross examination, the specimen consisted of a uterus with cervix and bilateral adnexa. The tumor was extensively involving the uterus and measured 16x7x4 cm. The tumor involved the body and fundus of the uterus, the lower uterine segment, and the cervix. On microscopic examination, the tumor had invaded full thickness through the myometrium with uterine serosal involvement; it was 0.2 cm from the paracervical margin. The tumor also involved the right fallopian tube and ovary. Bilateral parametria, omentum, the left fallopian tube, and the ovary were not involved. The morphology of the tumor was that of small cells, with high-grade nuclei, brisk mitosis, and tumor necrosis, which pointed towards a possible diagnosis of Small cell neuroendocrine carcinoma (**Fig. 2**). Other possible differential diagnoses considered were serous carcinoma, high-grade endometroid carcinoma, and metastatic small cell carcinoma. A panel of immunohistochemical antibodies was performed to confirm the diagnosis. The tumor cells were strongly positive for neuroendocrine markers Synaptophysin and CD56 (**Fig. 2**). Tumor cells showed characteristic dot positivity for pan-cytokeratin AE1/AE3, were positive for p53, indicating possible TP53 gene mutation, and showed a very high proliferative index of approximately 90% (**Fig. 3**). The tumor was negative for Estrogen Receptor (ER) and Wilms tumor (WT1), thus excluding endometroid and serous carcinomas. P16 stain, which is considered a surrogate marker for Human Papillomavirus infection in cervical cancers, was also negative. The tumor was also negative for metastatic markers from the lung, Thyroid Transcription Factor (TTF1) and gastrointestinal tract, CDX2, and Carcinoembryonic Antigen (CEA). Carcinosarcoma of the endometrium was also considered, but no heterologous stromal elements were identified. Thus, a diagnosis of SCNEC of primary uterine origin, FIGO stage IIIA, was rendered. Due to extensive tumor involvement of the uterus and the absence of any remaining normal mucosa, the origin of the tumor from either the endometrium or cervix could not be ascertained.

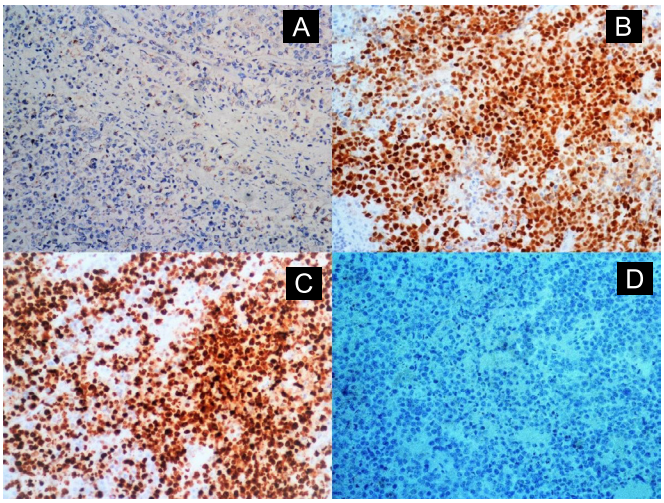

Fig. (3): **(A)** Cytokeratin AE1/AE3 stain, tumor cells show dot positivity. **(B)** Ki-67 stain, tumor cells show a high proliferative index. **(C)** P-53 stain, tumor cells show strong nuclear staining. **(D)** ER stain is negative.

After a discussion with the multidisciplinary team, chemotherapy consisting of Cisplatin and Etoposide was initiated. The patient and her attendants were counseled regarding the poor prognosis of the disease, complications of chemotherapy, and possible unfavorable outcomes of the tumor. Unfortunately, the patient died four months after the surgery because of pneumonia.

DISCUSSION

Small Cell Carcinoma is a type of neuroendocrine carcinoma; the lung is the most common primary tumor site. However, in the case of the female genital tract, SCNEC accounts for only 2% of all genital tract cancers, of which the cervix is the most common site of origin, followed by the ovary [3]. Incidence of vulvovaginal and endometrial cancers is even rarer, and SCNEC of the endometrium accounts for only 0.8% of all endometrial tumors [4]. SCNEC usually occurs in postmenopausal females, and patients mostly present with abnormal/irregular vaginal bleeding, but it can also present with a variety of paraneoplastic syndromes, including Cushing syndrome [5]. However, this aggressive tumor has been reported in women as young as 23 years in the literature [6]. SCNEC is considered a high-grade malignancy with potential for early invasion and metastasis and poor prognosis. Other types of neuroendocrine tumors include large-cell neuroendocrine carcinoma and low-grade neuroendocrine tumors, which can be differentiated based on their respective morphologies [7]. For the diagnosis of SCNEC, immunohistochemical antibodies serve as the confirmatory markers, and neuroendocrine

stains include synaptophysin, CD56, chromogranin A, and neuron-specific enolase [7]. Primary cervical neuroendocrine tumors have been reported to be associated with high-risk HPV infection with P16 overexpression [7]. Few cases have been reported to exhibit Alpha Fetoprotein positivity [8].

According to the guidelines of the European Consensus Conference, the treatment planning and staging for all gynecological cancers should be discussed in a multidisciplinary meeting and the patient should be counseled about the suggested treatment plan and prognosis [9]. Treatment should be provided in a specialized center equipped with a team of experts for managing gynecological cancers [9]. The first step for low-stage tumors remains surgery, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and lymphadenectomy, followed by chemotherapy and radiotherapy [3]. For higher-stage tumors, primary chemoradiation is advocated [3].

Despite the aggressive nature of the tumor, there are no specific guidelines, and the treatment regimen for small cell carcinoma of the lung is followed, which includes a combination of Etoposide and platinum-based agents such as Cisplatin and Carboplatin [10].

With the advent of new treatment modalities and targeted therapies, Bevacizumab has shown promising results in SCNEC of the cervix in the initial trials [11]. However, in the current era of targeted treatment, data for uterine tumors is still sparse, adding opportunity for future research.

CONCLUSION

SCNEC of the uterus remains one of the rare yet aggressive and invasive tumors. However, there is no established treatment strategy, and data is still scarce, leaving room for research and designing targeted therapies for neuroendocrine tumors. A multidisciplinary approach to treatment is advised, and patients should be counseled accordingly.

CONSENT FOR PUBLICATION

Informed consent was obtained from the participant of this study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Declared none.

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