

# An Extremely Rare Gynecologic Tumor; Pure Large-cell Neuroendocrine Carcinoma of the Endometrium: A Case Report

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**Abstract Introduction:** Pure large cell neuroendocrine carcinoma (LCNEC) of the endometrium is a rare and inadequately researched gynecologic malignancy with an aggressive course. Our knowledge of pure LCNEC of the endometrium is restricted to case reports. Herein, we describe a very rare case of pure LCNEC of the endometrium. **Case presentation:** A 70-year-old female presented with post-menopausal uterine bleeding and abdomino-pelvic pain. A sufficient sample endometrial biopsy showed benign endometrial tissue. We performed total abdominal hysterectomy with bilateral salpingo-oophorectomy and the final histopathology and immunohistochemistry established the diagnosis of a pure type of LCNEC of the endometrium (positive for Synaptophysin, CD56, focal Pan-CK, P53, and OCT3/4). **Conclusion:** A pure LCNEC of the endometrium is extremely uncommon and is often mistaken for a poorly differentiated endometrial carcinoma. Pure LCNEC of the endometrium is a difficult diagnosis to establish. That is why, high clinical suspicion index is required along with performing histological and immunohistochemical testing. Although rare, it is very important to include pure LCNEC of the endometrium in the differential diagnosis of abnormal uterine bleeding and/or abdomino-pelvic pain, especially in the postmenopausal sitting.

**Keywords:** pure large cell neuroendocrine carcinoma, endometrial cancer, abnormal uterine bleeding, Synaptophysin, CD56

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## 1. Introduction

Neuroendocrine cell tumors (NETs) are uncommon tumors that arise from cells of the neuroendocrine lineage. NETs are categorized into low-grade and high-grade tumors based on their pathological basis. However, NETs are also classified according to their differentiation level, ranging from well to poorly differentiated tumors [1]. Large cell neuroendocrine carcinoma (LCNEC) is an aggressive subclass of high-grade NETs. LCNEC most commonly originates in the thorax. However, it has also been reported to appear in the head and neck regions, the alimentary, hepatobiliary, genitourinary, and gynecologic tracts [2]. NETs of the female genital tract are rare and aggressive neoplasms that usually involve the cervix, ovary, or endometrium [3]. LCNEC of the endometrium is an extremely rare and aggressive malignancy that is often difficult to identify and treat. The first case of LCNET of the endometrium was recognized in 2004 [4]. LCNETs of

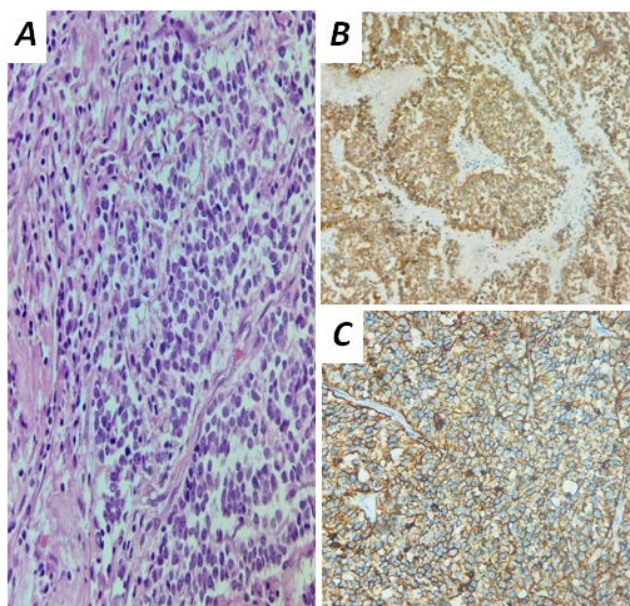
the endometrium resemble those of the lung in the context of histology and immunohistochemistry. In general, each neuroendocrine tumor (NET) typically expresses at least one neuroendocrine marker such as chromogranin, synaptophysin, NSE, and/or CD56 in more than 10% of malignant cells [5]. Due to the rarity of the disease, its management is still a mystery. However, surgery is the first line of management [6]. Herein, we report a case of endometrial pure LCNET. Broadening awareness of these unique malignancies could play a crucial role in their early detection and appropriate intervention.

## 2. Case Presentation

S.Q., a 70-year-old Palestinian married woman (gravida 5, para 4), with a body mass index (BMI) of 34, having no history of gynecologic abnormalities, came to our attention for the assessment of abnormal post-menopausal uterine bleeding and dull pelvic pain of two-month duration. Physical examination showed an enlargement of

the uterus. The laboratory evaluation was unremarkable and did not show anemia. Trans-vaginal ultrasound (TVUS) and computed tomography (CT) scan were performed and revealed an 11\*10 cm non-vascular mass in the endometrium; an enlarged uterus measuring 18 cm in longitudinal axis and 15 cm in transverse axis with increased endometrial wall thickness; cervix had a normal appearance, parametrium was free of disease, and no lymphadenopathy was detected. An endometrial biopsy was obtained and did not disclose any pathological features. On the 15<sup>th</sup> day following admission, the patient underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAHBSO) with regional lymph node dissection. She did not receive chemotherapy. The purpose of the surgical intervention was to eliminate the intra-abdominal tumor, which was causing her symptoms, and to obtain a definitive pathological diagnosis.

Grossly, the uterus was diffusely enlarged and the tumor necrotic mass seemed to arise from the endometrium, measuring 11\*10\*10 cm with about 90% of myometrial invasion. Uterine serosa, cervical stroma, fallopian tubes, and ovaries were not involved. Histologic examination of the uterine mass showed solid sheets of large cells with a moderate amount of cytoplasm and large nuclei. The mitotic count of the tumor cells was >10 per 10 high power field with marked necrosis. Immunohistochemistry demonstrated diffuse positivity for Synaptophysin, CD56, Pan-CK (focal), P53 (20%), and OCT3/4 (mainly cytoplasmic), and Immunonegativity for ER, CD10, WT1, PAX8, and SALL4. All of these features were consistent with a diagnosis of pure large cell neuroendocrine carcinoma (LCNEC) of the endometrium (Figure 1 A, B & C). The patient's postoperative 50-day period was uneventful, and the patient was disease free without receiving any adjuvant therapy during that period.



**Figure 1** (A). Histologic sample shows solid sheets of large cells with a moderate amount of cytoplasm and large nuclei with a mitotic count of the tumor cells >10 per 10 high power field. (B & C): immunohistochemical stains positive for Synaptophysin and CD56, respectively

### 3. Discussion

Large cell neuroendocrine carcinoma of the endometrium (LCNEC) is a very rare malignancy of the female genital tract. LCNEC is one of three primary types of endometrial neuroendocrine malignancies, which also include small cell neuroendocrine carcinoma (SCNEC) and carcinoid tumors [7]. The WHO defines LCNEC as a malignant tumor composed of large cells that show neuroendocrine differentiation [8].

The median age of presentation of LCNEC of the endometrium is 71 years at diagnosis [6], and the most common presenting symptom is postmenopausal vaginal bleeding [6]. In our case, the patient's age was 70 years, and she presented with postmenopausal vaginal bleeding, which is consistent with most reported cases.

Dilation and curettage were done, and the examined biopsy was not suggestive of neuroendocrine malignancy. The diagnosis of LCNEC by endometrial biopsy is challenging as it may be mistaken for other types of poorly differentiated endometrial malignancies [9]. The definitive diagnosis of LCNEC can only be made based on the histopathological examination of the resected tumor [10].

A preoperative lower abdominal computed tomography (CT) scan was done and showed uterine enlargement with a large endometrial mass. Total abdominal hysterectomy with bilateral salpingo-oophorectomy was done, with lymph node dissection. As in most cases of LCNEC, this one was diagnosed based on post-resection biopsy. Surgery is the first step in the management, which should involve at least hysterectomy and bilateral salpingo-oophorectomy (BSO) [6].

Post-operative management may include chemotherapy and/or radiotherapy [6]. There is no specific chemotherapy regimen for LCNEC, and cases are treated based on the treatment protocols of SCNEC for the lung [11]. Neoadjuvant chemotherapy may be considered in cases with preoperative diagnosis as surgical management is partially helpful [12].

The 2015 WHO classification of lung tumors describes the pathological features of LCNEC as large cells with a high nuclear to cytoplasmic ratio, high mitotic rates (>10 per 10 HPF), extensive tumor necrosis, positivity for one or more immunohistochemical neuroendocrine markers, and the presence of neuroendocrine growth patterns [13]. In this case, microscopic examination of the tumor revealed solid sheets of large cells with a moderate amount of cytoplasm and large nuclei. The mitotic count of the tumor cells was >10 per 10 high power fields with marked necrosis. The pathological examination of the uterus revealed a 90% invasion of the myometrium with free serosa. Both fallopian tubes, ovaries, cervical stroma, lower uterine segment, and all regional lymph nodes were free of malignancy. The examined lymph nodes were the right and left common iliac lymph nodes and the left external iliac lymph nodes.

Immunohistochemical staining is the best diagnostic tool for LCNEC, with synaptophysin, chromogranin, and CD56 being the most commonly used. LCNEC is aggressive in its nature, and most cases are present at late

stages with distant metastasis. It is characterized by rapid progression, poor prognosis, and/or post operative recurrence [14].

## 4. Conclusion

Pure large cell neuroendocrine carcinoma (LCNEC) of the endometrium is an extremely rare female reproductive tract malignancy with an aggressive course. The most common clinical presentation of pure LCNEC of the endometrium is abnormal uterine bleeding with or without abdominosa-pelvic pain. Endometrial biopsy is usually non-diagnostic. LCNEC of the endometrium is often mistaken for poorly differentiated endometrial carcinomas. Therefore, histo-pathological findings and immunohistochemistry are necessary in establishing a diagnosis of LCNEC of the endometrium. In this case study, we affirm the significance of suspecting LCNEC of the endometrium in women complaining of abnormal uterine bleeding and/or abdomino-pelvic pain, especially in the postmenopausal period.

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