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Primary Small Cell Neuroendocrine Carcinoma of the Endometrium: A Cytologically Diagnosed Case with Immunocytochemical, Immunohistochemical, and Electron Microscopic Features

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Abstract

Endometrial neuroendocrine tumors are rare, accounting less than 1% of endometrial cancers. They include small cell neuroendocrine carcinoma (NEC) and large cell NEC and usually occur in postmenopausal patients. Although common symptoms include postmenopausal bleeding, most patients are diagnosed at an advanced stage. We report an extremely rare case of small cell NEC developed in the endometrium of a 75-year-old Japanese woman. This case was initially suspected based on the findings of endometrial cytology: a number of small round malignant cells were present on the endometrial smear specimens. The immunocytochemical and immunohistochemical examinations revealed diffusely cytoplasmic positive reaction of neuron specific enolase (NSE) and partially membranous positive reaction of CD56 in the small cancer cells. They showed PAX-8-positive reaction, but did not express microsatellite instability high. Electron micrography showed several dense-core secretory granules in the cytoplasm of cancer cells. Despite multiple lung metastases, the patient underwent a hysterectomy and salpingo-oophorectomy in order to control excessive genital bleeding. She received six courses of adjuvant chemotherapy based on etoposide and cisplatin, and survived healthy

eight months after the first visit without any viability of lung metastases.

Keywords

SCNEC, Endometrium, NSE, Ultrastructure, Etoposide and Cisplatin Regimen

1. Introduction

Neuroendocrine tumors could occur in the female genital organs, but endometrial neuroendocrine tumors are extremely rare. According to the recent WHO classification, they are categorized as low-grade and high-grade neuroendocrine neuroendocrine carcinomas [1]. They are further sub-classified into small-cell and large-cell types [1] [2]. Approximate 100 cases of small-cell neuroendocrine carcinoma (SCNEC) of the endometrium have been reported in the English literatures [3] [4] [5] [6]. SCNEC of the endometrium demonstrates aggressive clinical behavior [1] [4] [5] [7]. Endometrial SCNEC is known to be highly aggressive, because this malignancy is usually diagnosed at advanced stages of the diseases [8]. Furthermore, the prognosis of a pure type of SCNEC is worse, when comparing to that of a mixed type of SCNEC [9].

While most of the SCNECs of the uterine cervix possess mutations in *PIK*3*CA*, *K-ras*, and *p*53, molecular pathology of the endometrial SCNECs is unknown [10]. Abnormal mismatch repair protein expression was described in a few cases of endometrial SCNECs, but the majority of reported cases have not been included mismatch repair testing [5].

Endometrial cytological examination is a useful and minimally invasive tool for detecting endometrial malignancies, premalignancies, and benign lesions [11]. However, studies on the cytological features of SCNECs of the endometrium are scare [3] [4]. In the present report, we describe cytological, immunocytochemical, immunohistochemical, and ultrastructural features of endometrial SCNEC developed in an old Japanese woman, her clinical course as well.

2. Case Presentation

A 75-year-old female, gravida four para four, presented to our hospital with vaginal bleeding for more than three months in 20xy. She had a slight dementia due to previous cerebral bleeding, but did not have chronic diseases, such as hypertension, diabetes. The patient had inserted a soft pessary due to complete prolapse uteri three years ago. She did not visit the gynecologic clinic until then. When the pessary in the vagina was removed, we found that the bleeding came from the uterine cavity. The uterine corpus was enlarged as over new born head size. The endometrial cytology and curettage were performed. On the endometrial cytology specimens, we found atypical cells suggestive of SCNEC [**Figure**

1(a)]. Immunocytochemistry revealed that they showed strongly cytoplasmic reactivity against neuron-specific enolase (NSE) [Figure 1(b)]. Endometrial curettage histological specimens were fixed in 10% neutral buffered formalin, routinely processed, and embedded in paraffin for histopathology and immunohistochemistry. Sections with 3 - 4 μm thickness were made and stained with hematoxylin and eosin (H&E) for histopathological diagnosis. Immunohistochemistry using twelve different antibodies, such as AE1/AE3 [Dako, 1:50 dilution], NSE (Dako, 1:400 dilution), CD56 (Dako, 1:100 dilution), synaptophysin (Dako, 1:20 dilution), thyroid transcription factor-1 (TTF-1, DAKO, 1:100 dilution), chromogranin (DAKO, 1:1600 dilution), Pax-8 (Protein Tech, 1:100 dilution), MSH2 (Calbiochem, 1:100 dilution), MLH1 (Cell Marque, 1:300 dilution), MSH6 (BD Biosciences, 1:300 dilution), PMS2 (BD Biosciences, 1:125 dilution), and p53 (Dako, 1:100 dilution) was performed. Histopathological examination confirmed SCNEC of the endometrium [Figure 2(a)]. Immunohistochemically, cytoplasm of the tumor cells was strongly positive for NSE [Figure 2(b)]. We also observed nuclear positivity of TTF-1 [Figure 2(c)] and partially cell membranous positivity of CD56 [Figure 2(d)]. Pax-8 [Figure 2(e)], MSH2 [Figure 2(f)], MLH1, MSH6, and PMS2 were all positive in the nucleus of the tumor cells. p53 was partially positive in the tumor cell nuclei.

For electron microscopic examination, small pieces of the formalin-fixed neoplastic tissues were re-fixed in 1% osmium tetroxide, followed by 0.2 M phosphate buffer, and then embedded in epoxy resin. Ultrathin sections were examined using an electron microscope after staining with uranyl acetate and lead citrate. Ultrastructurally, the cytoplasm of small neoplastic cells contained electron-dense core secretory granules with approximately 500 nm in diameter (Figure 3) in the cytoplasm.

We determined DNA repair function of the tumor cells using the MSI-IVD Kit (FALCO Biosystems, Kyoto, Japan), which is able to detect MSI-High status within tumor tissues [12]. However, MSI-high could not be detected (Figure 4), as found in immunohistochemistry of MSH2, MLH1, MSH6, and PMS2.

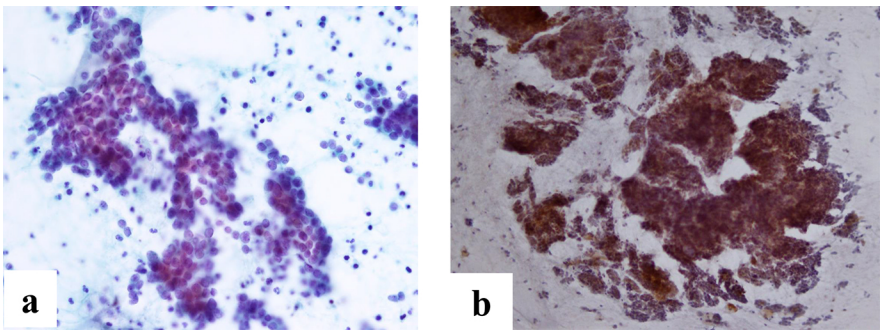

Figure 1. Endometrial cytology. (a) Aggregates of small neoplastic cells with high N/C ratio are present. (b) Neuron-specific enolase (NSE)-immunocytochemistry shows strong cytoplasmic positive reaction in the tumor cells. (a) Papanicolaou stain, ×100; and (b), NSE immunocytochemistry, ×100.

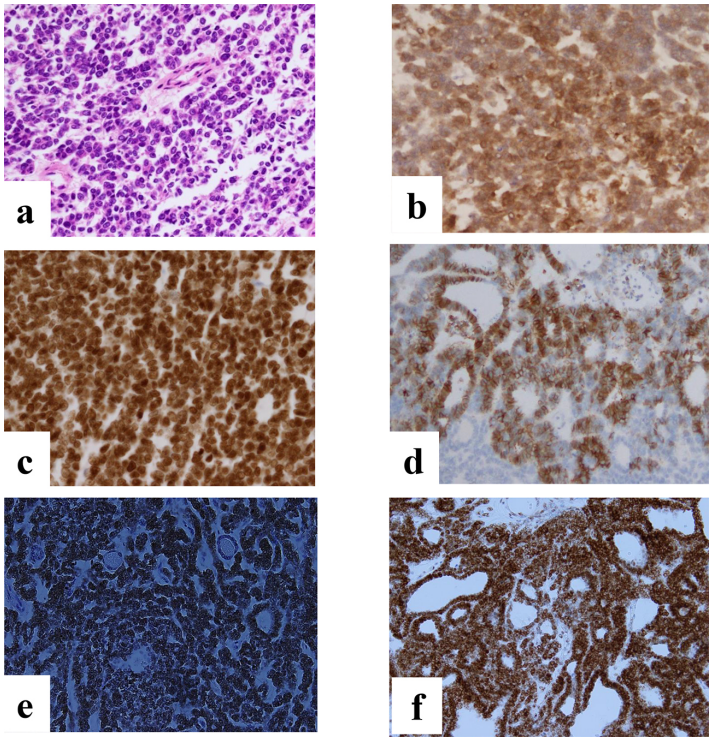

Figure 2. Histopathology and immunohistochemistry of specimens obtained by endometrial curettage. (a) Small neoplastic cells having scant cytoplasm and hyperchromatic round to oval nuclei without visible nucleoli grow in sheets or trabeculas. Immunohistochemical stainings show cytoplasmic positivity of (b) NSE, nuclear positivity of (c) TTF-1, partial membranous positivity of (d) CD56, nuclear positivity of (e) PAX8, and nuclear positivity of (f) MSH2 in the neoplastic cells. (a) H&E stain, ×100; (b) NSE immunohistochemistry, ×100; (c) TTF-1 immunohistochemistry, ×100; (d) CD56 immunohistochemistry, ×100); (e) PAX-8 immunohistochemistry, ×80; and (f) MSH2 immunohistochemistry, ×100.

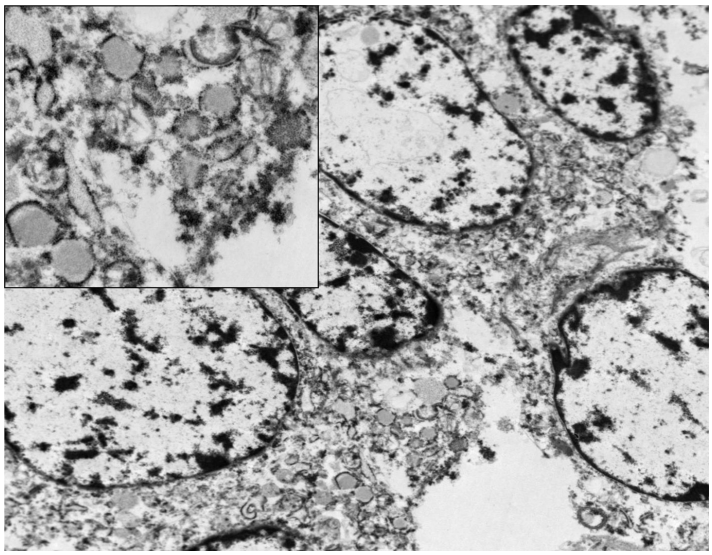

Figure 3. Electron microscopy reveals that small cancer cells have dense-core secretory granules (insert), measuring approximately 500 nm in diameter, in their cytoplasm. Magnification ×13,000.

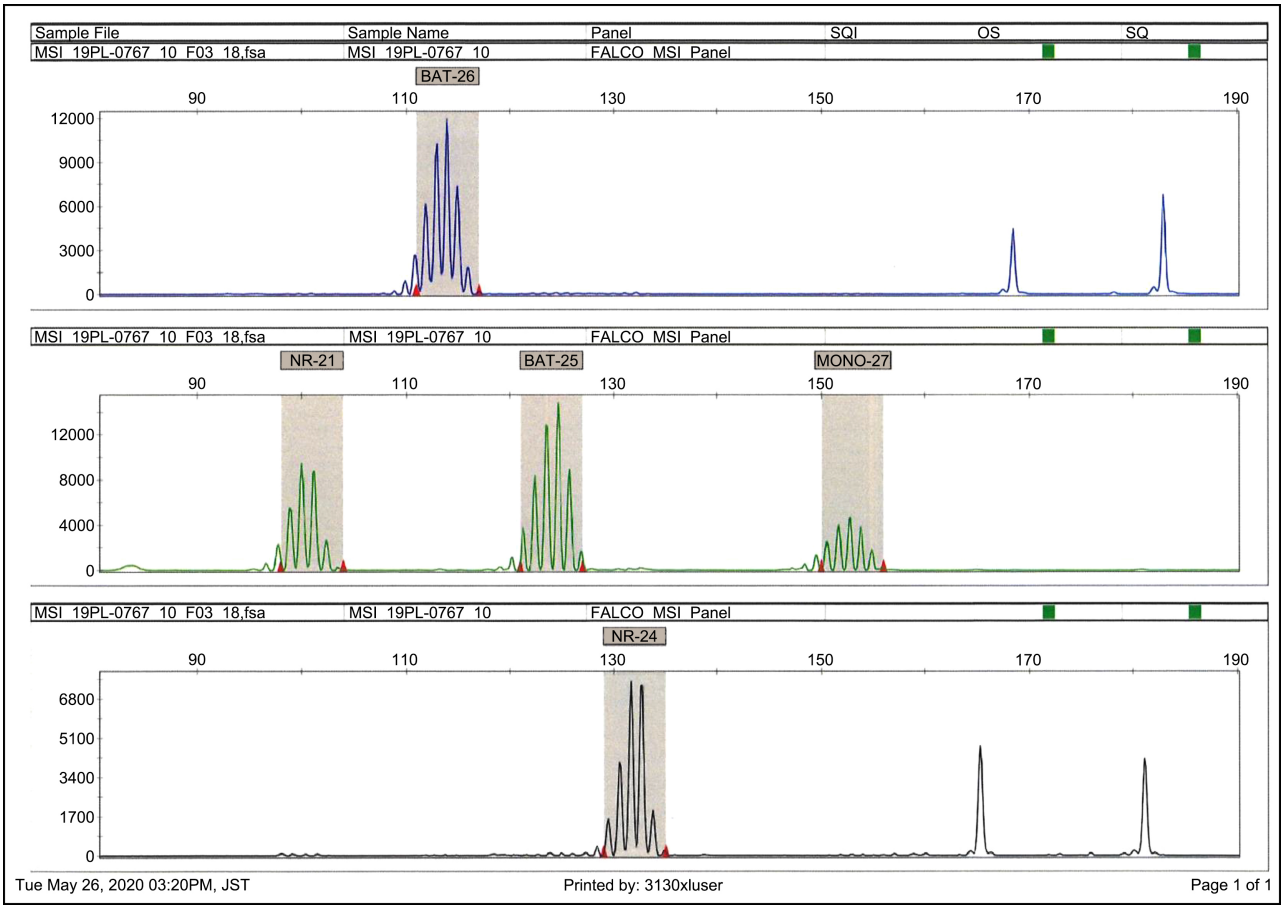

Figure 4. MSI detection pattern. Single symmetric peak was observed in each quasi-monomorphic variation range, suggesting MSI-negative in the tumor cells.

The tumor was suspected to invade to the almost entire wall on magnetic resonance imaging (MRI) (**Figure 5**), and the whole body computed tomography (CT) scan showed multiple lung metastases [**Figure 6(a)**]. Therefore, clinical stage was stage IVB. The patient underwent an operation due to uncontrolled genital bleeding two weeks after the first visit. Serum tumor markers, such as CA125, CA19-9, α-fetoprotein, and NSE were within normal limits. A hysterectomy and bilateral salpingo-oophorectomy were performed without resection of pelvic lymph nodes, because no metastases in the pelvic lymph nodes were noted on the MRI and CT scans. Small amount of ascites, which did not contain cancer cells was observed during operation. Histopathological examinations revealed confirmed pure SCNEC of the endometrium, and other histologically different neoplasms were not detected. The uterine corpus was almost replaced by the tumor, but the tumor did not invade the serosa (**Figure 7**) and surrounding tissues, including vagina and lymph nodes. The tumor containing bleeding and necrotic areas in parts was yellowish and relatively soft.

The patient showed uneventful clinical course after the operation. Two weeks after the operation, she started the systemic chemotherapy with etoposide and cisplatin (EP) regimen, which is the adjuvant treatment used for uterine cervical

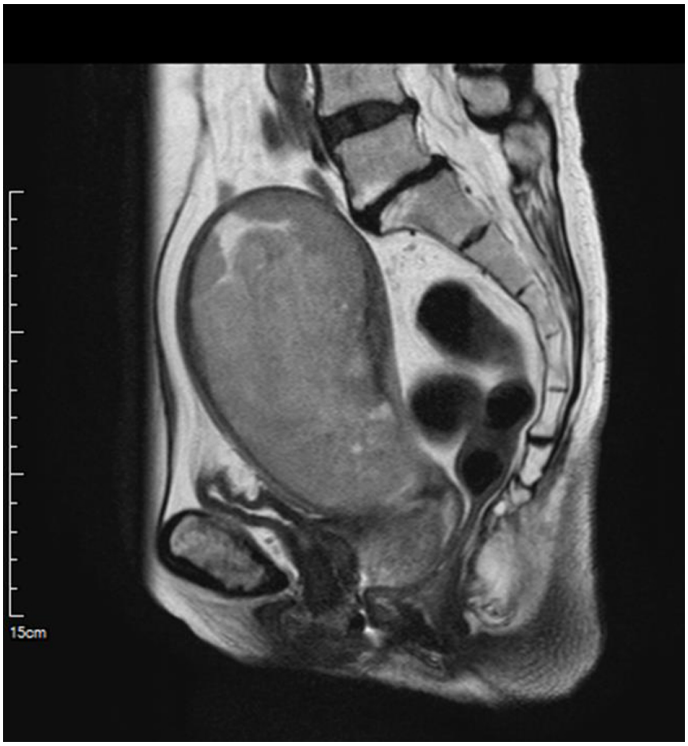

Figure 5. Sagital T2-weighted MR image showing a large tumor with a heterogeneously high intensity, which replaces the cavity of uterine corpus. The tumor measures 110 mm in major axis.

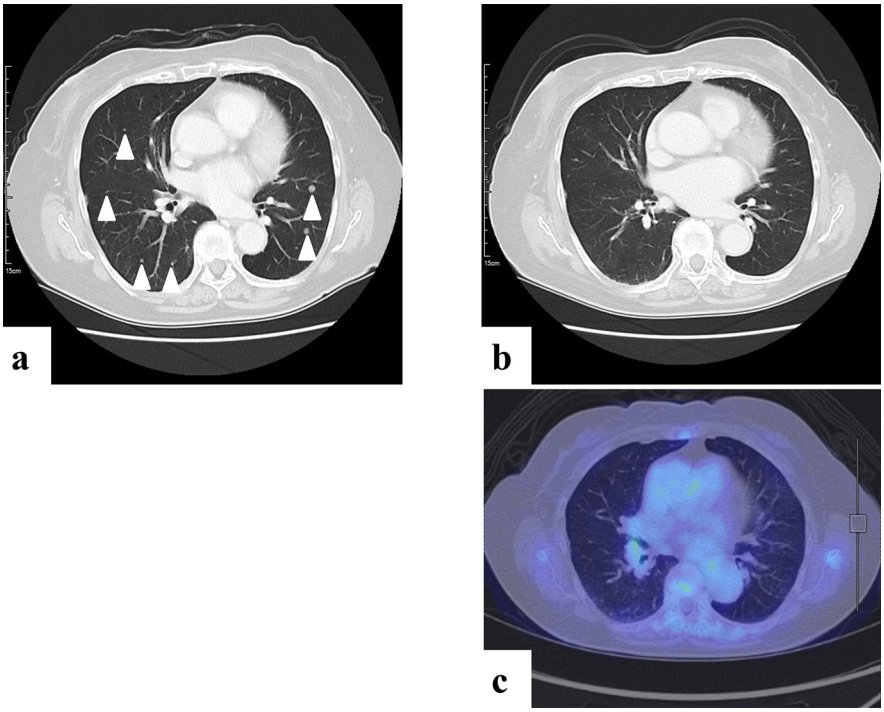

Figure 6. Lung CT and FDG-PET/CT images. (a) Lung CT image before the chemotherapy shows multiple small metastatic lesions (arrow heads). (b) Metastatic lesions are not present on the lung CT image 6-course after the chemotherapy. (c) The FDG-PET/CT shows no enhanced FDG uptake in the lungs.

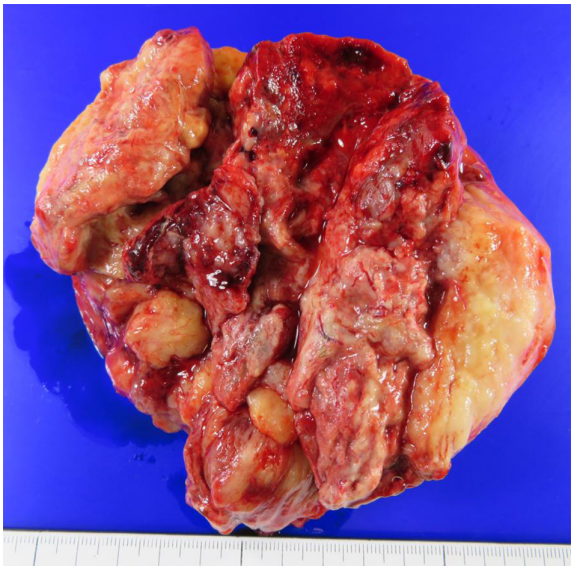

Figure 7. Macroscopic view of the uterus resected surgically. A tumor occupies the endometrial cavity and invades the myometrium, but the serosa is intact. Bleeding and necrotic areas are present in the yellowish and relatively soft tumors.

SCNEC [13] [14]. Because of her higher age, the dosages were reduced: daily etoposide 75 mg/m^2 on day 1, 2, and 3, and cisplatin 40 mg/m^2 on day 1. This regimen is administered for six cycles at 21-day intervals, resulting in disappear of lung metastases [**Figure 6(b)**] and FDG-ET/CT examination confirmed no viability of tumor cells in the lungs [**Figure 6(c)**]. The patient survived healthy eight months after the first visit.

3. Discussion

The primary SCNEC of the endometrium, which was reported to be approximately 100 cases in the literature is an extremely rare neoplasm [3] [4] [5] [6]. Mean age at the diagnosis is over 60, our case being 75-year-old. Abnormal or postmenopausal bleeding is the most frequent symptom, as experienced in this case [15]. The cytological and clinicopathological characteristics, including electron microscopic findings and a variety of immunohistochemical features of primary endometrial SCNEC are described. In addition, the management and clinical outcomes of our patient are also presented. We also determined DNA repair function of cancer cells using the MSI-IVD Kit and immunohistochemistry with primary antibodies, such as MSH2, MLH1, MSH6, and PMS2. However, cancer cells did not have DNA repair dysfunction.

The endometrial SCNEC is reported to have aggressive clinical behavior [1, 7]. Five-year survival rate of stage IVB in ENCs was found to be 12.0% (0.7% - 40.8%), while that of endometrioid adenocarcinoma was 27.7% (25.2% - 30.3%) [6]. The aggressive surgical resection and adjuvant chemotherapy with or without radiotherapy appeared to be responsible for the favorable outcomes. Our

case was histopathologically a pure type of endometrial SCNEC. When compared to a mixed type of endometrial SCNEC, prognosis of a pure type was reported to be worse [9]. Treatment strategies for endometrial NEC are not standardized [6], and most cases of endometrial SCNEC include platinum-based chemotherapy with etoposide or paclitaxel [6] [15], as performed in the small cell lung cancers. In our case, reductive surgery and following EP chemotherapy suppressed recurrence and lung metastases.

There are a few reports on the cytological features of endometrial SCNEC [3] [4]. The characteristics of cytological include the presence of single or small nests of neoplastic cells with a high nuclear/cytoplasmic ratio, round to oval nuclei containing coarse chromatin in necrotic backgrounds [3], corresponding to the typical cytological features of lung SCNEC [16]. As reported [17], immunocytochemistry using NSE was useful for the cytological diagnosis of endometrial SCNEC in this case.

For accurate histopathological diagnosis of NEC, neuroendocrine markers, including NSE, chrogranin A, synaptophsin, Leu-7, and CD56 are essential [18] [19]. All NECs expressed at least one neuroendocrine marker [1] [5] [7]. In this case, the cancer cells showed cytoplasmic positive reaction of NSE and partially cell membranous positivity of CD56. Electron microscopic findings showing cytoplasmic electron-dense secretory core granules in cancer cells confirmed neuroendocrine features of the neoplasm in this case [20].

Although a transcription factor, PAX-8, in the regulation of organogenesis of the thyroid gland, kidney, and Müllerian system, is commonly expressed in the nuclei of most endometrial adenocarcinoma cells [21], approximate 30% of endometrial NECs were immunohistochemically positive for PAX-8 [5]. Pocrnich *et al.* reported that the NECs tend to be PAX-8 negative and may be associated with microsatellite instability [5]. However, their cases were large cell NECs. In our case, PAX-8 was positive and p53 was focally positive in the cancer cell nuclei. It is known that nuclear expression of PAX-8 and p53 is well-correlated in the endometrial carcinomas regardless histopathological types such as endometrioid and non-endometrioid types. Pax-8 positivity correlating with p53 expression might be one of useful prognostic parameters [22]. Most commonly observed mutations were reported to be *PIK3CA*, *K-ras*, and *p53* in the SCNEC of the uterine cervix [23] [24] [25], the molecular alterations in the endometrial SCNEC were not well-understood because of its rarity [10]. Nuclear p53 was focally positive in the tumor cells, suggesting the importance of p53 mutation for the development of SCNEC in our case.

4. Conclusion

We report here an extremely rare case of primary endometrial SCNEC initially diagnosed by endometrial cytology. Immunocytochemical, immunohistochemical, and ultrastructural examinations confirmed the diagnosis. Reductive surgery and EP-chemotherapy were effective for the treatment.

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Authors' Contributions

Authors' contributions	KNi	KNa	SM	KK	MM	MT	YY	KNi	TT
Research concept and design	y	n	n	n	n	n	n	y	n
Collection and/or assembly of data	y	y	y	n	n	y	y	y	n
Data analysis and interpretation	y	y	y	y	y	y	y	y	n
Writing the article	y	n	n	n	n	n	n	n	y
Critical revision of the article	y	n	n	n	n	n	n	n	y
Final approval of the article	y	y	y	y	y	y	y	y	y

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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