

Brief Communication

Small cell carcinoma of the endometrium: a case report with emphasis on the cytological features

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Small cell carcinoma (SCC) is a distinct clinico-pathological entity, and the most common site is the lung, although less frequently, it can also occur in a variety of sites including the gastrointestinal tract. The occurrence of SCC in the genital tract is rare, and most of the cases were found in the uterine cervix and ovary. Primary SCC is an extremely rare type of carcinoma of the endometrium, accounting for approximately 0.8% of all endometrial carcinomas [1]. Approximately 80 cases of endometrial SCC have been reported in the English-language literature [2-33].

Endometrial cytological examination is a useful and minimally-invasive tool for detecting endometrial malignancies and variety of premalignant and benign lesions [34, 35]. Thus far, only one cytological report of endometrial SCC has been documented in the English-language literature [36]. Herein, we describe a case of primary SCC of the endometrium with emphasis on the cytological features of the endometrium and ascites.

An 80-year-old Japanese female (1 gravida and 1 partus) presented with abdominal pain at an outpatient clinic. Magnetic resonance imaging demonstrated a tumorous lesion in the uterus (mixture of low and high intensity areas in the muscular layer on T2 imaging) involving the right ureter, which led to hydronephrosis of the right kidney and swelling of the left intrapelvic lymph nodes. No tumorous lesion was detected in the lung. She was referred to our hospital for

operation. Laboratory tests revealed an elevated level of lactate dehydrogenase (1,194 U/L (range 119-229)) and slightly elevated level of CA19-9 (51 U/mL (<37)), however other tumor markers were within normal ranges (carcinoembryonic antigen 4.0 ng/mL (<5.0), CA125 30 U/mL (<35), and SCC 0.5 ng/mL (<1.5). Cytological examination of the endometrium was performed.

Subsequently, she underwent total hysterectomy and bilateral salpingo-oophorectomy with resection of the sigmoid colon and dissection of the pelvic lymph nodes. Cytological examination of the ascites was also performed. The post-operative course was uneventful, and chemotherapy (paclitaxel and carboplatin) was performed.

The cytological specimen of the endometrium demonstrated abundant single or small clusters of neoplastic cells in a necrotic background (**Figure 1A**). These neoplastic cells had scant cytoplasm, and round to oval nuclei with coarse chromatin and inconspicuous nucleoli (**Figure 1B, 1C**). Nuclear molding was prominent, and mitotic figures and apoptotic bodies were scattered (**Figure 1B, 1C**). No conventional adenocarcinoma component was present. Accordingly, a cytodiagnosis of SCC was made.

The histopathological study of the resected uterus specimen revealed sheet-like or variably-sized nest-like proliferation of small round cells with or without central necrosis involving the

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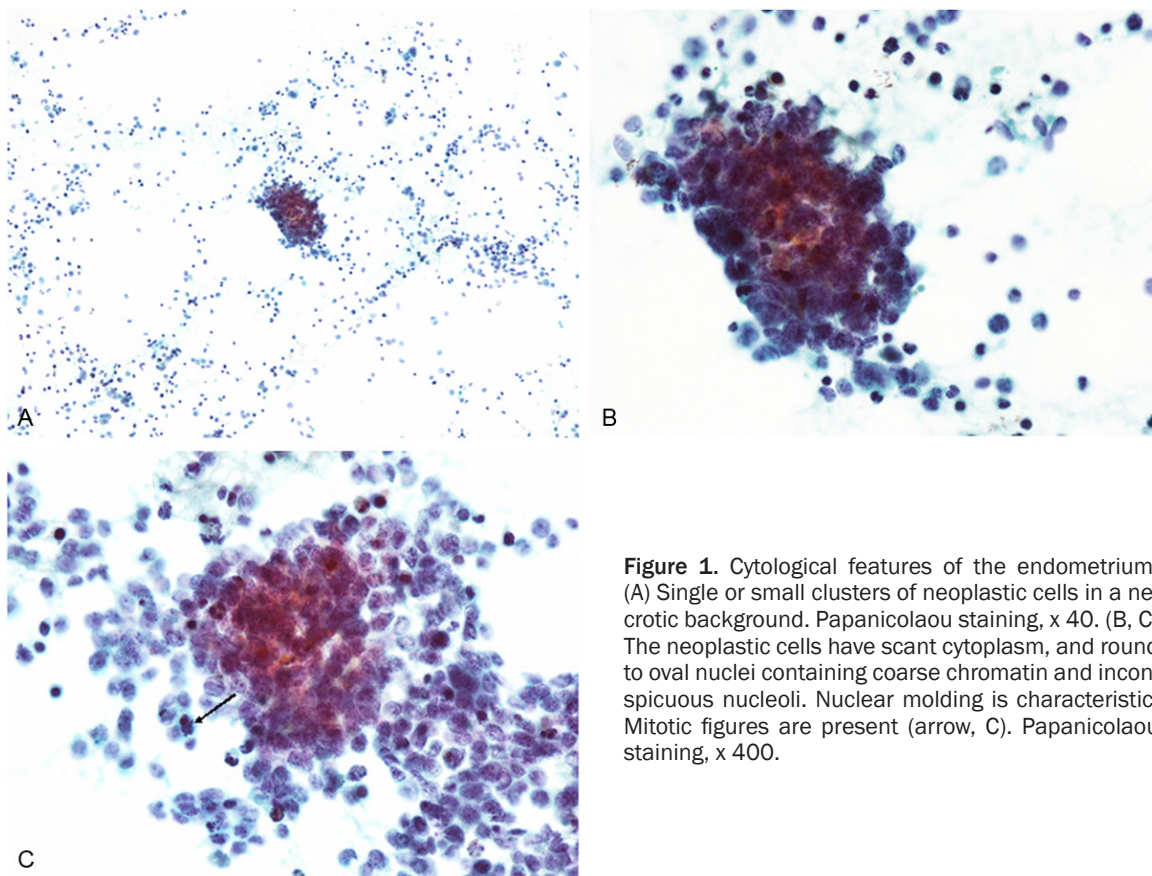


Figure 1. Cytological features of the endometrium. (A) Single or small clusters of neoplastic cells in a necrotic background. Papanicolaou staining, x 40. (B, C) The neoplastic cells have scant cytoplasm, and round to oval nuclei containing coarse chromatin and inconspicuous nucleoli. Nuclear molding is characteristic. Mitotic figures are present (arrow, C). Papanicolaou staining, x 400.

surface endometrium to the entire uterus wall (**Figure 2A**). These neoplastic cells had high nuclear/cytoplasmic ratio, and round to oval nuclei containing coarse chromatin and inconspicuous nucleoli (**Figure 2B**). Abundant apoptotic bodies and mitotic figures were observed (47/10 high-power fields). Approximately 97% of the tumor was the above-mentioned SCC component, and a small focus of endometrioid adenocarcinoma component, which was composed of tubular glands with large round to oval nuclei, was present in the surface of the endometrium contiguous to the SCC component (**Figure 2C, 2D**). Metastatic small cell carcinoma was observed in the bilateral ovaries and left pelvic lymph nodes. Moreover, invasion of SCC was also noted from the serosa to subserosa of the sigmoid colon.

Immunohistochemical studies were performed using an autostainer (Ventana) by the same method as previously reported [37-41]. Synaptophysin and CD56 were diffusely expressed in the SCC component (**Figure 2E**), but negative in the adenocarcinoma compo-

nent. Chromogranin A-positive neoplastic cells were present in the SCC component (**Figure 2F**), and a few chromogranin A-positive adenocarcinoma cells were also noted (**Figure 2F**, inset). TTF-1 was negative in both component.

Accordingly, an ultimate diagnosis of SCC with endometrioid adenocarcinoma component of the uterus (pT4aN1M0, stage IVA) was made.

The cytological specimen of the ascites showed single or small clusters of neoplastic cells (**Figure 3A**). These neoplastic cells had scant cytoplasm, and round to oval nuclei with coarse chromatin and inconspicuous nucleoli (**Figure 3B**). No conventional adenocarcinoma component was present. Accordingly, a cytodiagnosis of SCC was made.

Primary SCC of the endometrium is an extremely rare tumor, and we summarized the clinicopathological features of this type of tumor [2-33], as follows: i) this type of carcinoma mainly affects the elderly [5], however, a few cases occurring in young females have also been documented [2, 32]; ii) approximately half

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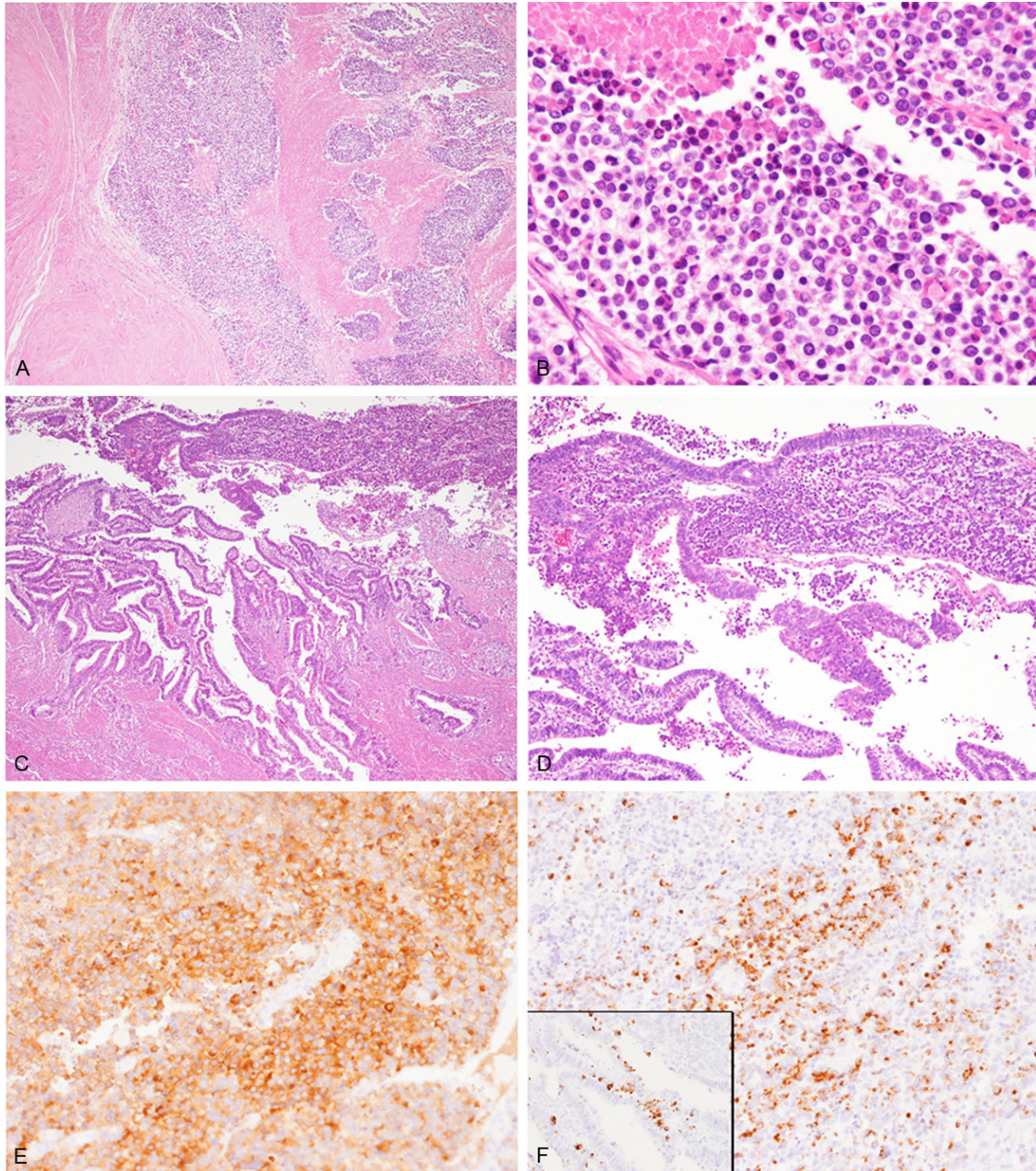


Figure 2. Histopathological and immunohistochemical features of the uterus tumor. A. Proliferation of small round cells with necrosis invading into the muscular layer of the uterus. HE, x 40. B. The neoplastic cells have scant cytoplasm, and round to oval nuclei containing coarse chromatin and inconspicuous nucleoli. HE, x 400. C. An endometrioid adenocarcinoma component is present adjacent to the small cell carcinoma in the surface of the endometrium. HE, x 40. D. The adenocarcinoma has large round to oval nuclei. HE, x 200. E. Synaptophysin is diffusely expressed in the small cell carcinoma component. x 400. F. Chromogranin A is also expressed in the small cell carcinoma component. A few chromogranin A-positive cells are present in the adenocarcinoma (inset). x 400.

of the cases were stage III or IV at initial presentation, and the median survival for these patients was only 5 months [5, 27]; iii) the presence of other types of carcinoma components, as seen in the present case, is frequently

described, and the most common histopathological subtype is endometrioid adenocarcinoma, although adenosquamous and serous adenocarcinomas as well as malignant mixed müllerian tumor have also been reported [5, 7,

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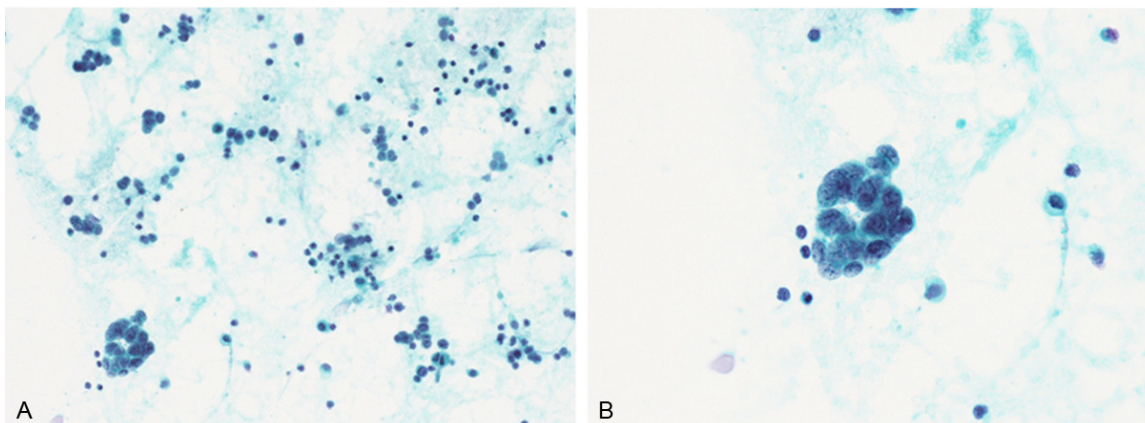


Figure 3. Cytological features of the ascites. A. Single or small clusters of the neoplastic cells are observed. Papanicolaou staining, x 40. B. The neoplastic cells have scant cytoplasm and round to oval nuclei containing coarse chromatin and inconspicuous nucleoli. Nuclear molding is characteristic. Papanicolaou staining, x 400.

8, 10, 17, 18, 24, 27, 29]; and iv) paraneoplastic syndromes, such as ocular retinopathy and Cushing's syndrome, have been reported to be associated with endometrial SCC [7, 14, 20, 24, 25].

SCC of the endometrium must be differentiated from metastatic SCC from the other organs, such as the lung. In the present case, preoperative surveillance failed to detect any tumorous lesions in the lung, which is the most common site of SCC. Moreover, an endometrioid adenocarcinoma component was present in the surface of the endometrium. These results facilitated the ultimate diagnosis of primary SCC of the endometrium. In the largest series of 16 cases of endometrial SCC reported by Huntsman *et al.*, 8 cases had endometrioid adenocarcinoma component and 2 cases had atypical complex hyperplasia [27]. Therefore, detection of combined carcinoma or premalignant lesion of the endometrium is important for determining whether SCC in the endometrium is primary or metastatic.

Proca *et al.* first described the cytological features of two cases of SCC of the endometrium [36]. The cytological features of their two cases and the present one were fundamentally the same as those of SCC of the lung, as follows: i) the presence of single or small nests of neoplastic cells in a necrotic background; ii) the neoplastic cells have a high/nuclear cytoplasmic ratio and round to oval nuclei containing coarse chromatin and inconspicuous nucleoli; and iii) nuclear molding is characteristic [36].

Therefore, it is necessary for cytologists and cytopathologists to keep in mind that SCC can occur in the genital tract including the endometrium and the characteristic cytological features can lead to the correct diagnosis because this type of tumor shows a highly aggressive clinical course.

Disclosure of conflict of interest

None.

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References

- [1] Abeler VM, Kjorstad KE, Nesland JM. Undifferentiated carcinoma of the endometrium: a histopathologic and clinical study of 31 cases. *Cancer* 1991; 68: 98-105.
- [2] Ureyen I, Karalok A, Turan T, Boran N, Tapisiz OL, Okten H, Kose MF, Tulunay G. Small cell carcinoma of the endometrium: a report of three cases. *J Turk Ger Gynecol Assoc* 2013; 14: 113-115.
- [3] Abaid LN, Cupp JS, Brown JV 3rd, Goldstein BH. Primary small cell neuroendocrine carcinoma of the endometrium. *Case Rep Oncol* 2012; 5: 439-443.
- [4] Kurtay G, Taskin S, Kadan E, Sertcelik A. Primary endometrial small cell carcinoma. *J Obstet Gynaecol* 2012; 32: 104-106.

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- [5] Matsumoto H, Takai N, Nasu K, Narahara H. Small cell carcinoma of the endometrium: a report of two cases. *J Obstet Gynaecol Res* 2011; 11: 1739-1743.
- [6] Terada T. KIT-positive primary small cell carcinoma of the endometrium: a case report with immunohistochemical and molecular genetic analysis of KIT and PDGFRA genes. *Arch Gynecol Obstet* 2010; 282: 413-416.
- [7] Sato H, Kanai G, Kajiwara H, Itoh J, Osamura RY. Small-cell carcinoma of the endometrium presenting as Cushing's syndrome. *Endocr J* 2010; 57: 31-38.
- [8] Hwang JH, Lee JK, Lee NW, Lee KW. Primary small cell carcinoma of the endometrium: report of a case with immunohistochemical studies. *J Reprod Med* 2010; 55: 81-86.
- [9] Bahig H, Portelance L, Legler C, Gilbert L, Souhami L. Small cell carcinoma of the endometrium: report of a case and review of the literature. *Minerva Ginecol* 2009; 61: 365-369.
- [10] Albores-Saavedra J, Martinez-Benitez B, Luevano E. Small cell carcinomas and large cell neuroendocrine carcinomas of the endometrium and cervix: polypoid tumors and those arising in polyps may have a favorable prognosis. *Int J Gynecol Pathol* 2008; 27: 333-339.
- [11] Bige O, Saatli B, Koyuncuoglu M, Saygili U. Small cell neuroendocrine carcinoma of the endometrium and laparoscopic staging: a clinicopathologic study of a case and a brief review of the literature. *Int J Gynecol Cancer* 2008; 18: 838-843.
- [12] Korcum AF, Aksu G, Ozdogan M, Erdogan G, Taskin O. Stage I small cell carcinoma of the endometrium: survival and management options. *Acta Obstet Gynecol Scand* 2008; 87: 122-126.
- [13] Melgoza F, Brewster WR, Wilczynski S, Rutgers J. p16-positive small cell neuroendocrine carcinoma of the endometrium. *Int J Gynecol Pathol* 2006; 25: 252-256.
- [14] Ju W, Park IA, Kim SH, Lee SE, Kim SC. Small cell carcinoma of the uterine corpus manifesting with visual dysfunction. *Gynecol Oncol* 2005; 99: 504-506.
- [15] Rajab KE, Sandhu AK, Malik A, Rajeswari MS. Small cell neuroendocrine carcinoma of the endometrium, a rare aggressive tumor. *Saudi Med J* 2005; 26: 1130-1132.
- [16] Stachs A, Makovitzky J, Briese V. Small cell carcinoma of the endometrium: light microscopic and immunohistochemical study of a case. *Anticancer Res* 2005; 25: 1823-1826.
- [17] Shaco-Levy R, Manor E, Piura B, Ariel I. An unusual composite endometrial tumor combining papillary serous carcinoma and small cell carcinoma. *Am J Surg Pathol* 2004; 28: 1103-1106.
- [18] Katahira A, Akahira J, Niikura J, Ito K, Moriya T, Matuzawa S, Makinoda S, Oda T, Fujiwara K, Yaegashi N. Small cell carcinoma of the endometrium: report of three cases and literature review. *Int J Gynecol Cancer* 2004; 14: 1018-1023.
- [19] Meirmanov S, Nakashima M, Rogounovitch T, Fukuda E, Nakayama T, Sato F, Sekine I. Small cell carcinoma of the endometrium: report of a case with analysis of Wnt/beta-catenin pathway. *Pathol Res Pract* 2003; 199: 551-558.
- [20] Meydanli MM, Erguvan R, Altinok MT, Ataoglu O, Kafkasli A. Rare case of neuroendocrine small cell carcinoma of the endometrium with paraneoplastic membranous glomerulonephritis. *Tumori* 2003; 89: 213-217.
- [21] Varras M, Akrivis Ch, Demou A, Hadjopoulos G, Stefanaki S, Antoniou N. Primary small-cell carcinoma of the endometrium: Chuang J, Chu CC, Hwang JL, Cheng WC. Small cell carcinoma of the endometrium with concomitant pelvic inflammatory disease. *Arch Gynecol Obstet* 2002; 266: 178-180.
- [22] Chuang J, Chu CC, Hwang JL, Cheng WC. Small cell carcinoma of the endometrium with concomitant pelvic inflammatory disease. *Arch Gynecol Obstet* 2002; 266: 178-180.
- [23] Verchraegen CF, Matei C, Loyer E, Malpica A, Tornos C, Kudelka AP, Kavanagh JJ. Octreotide induced remission of a refractory small cell carcinoma of the endometrium. *Int J Gynecol Cancer* 1999; 9: 80-85.
- [24] Sekiguchi I, Suzuki M, Sato I, Ohkawa T, Kawashima H, Tsuchida S. Rare case of small-cell carcinoma arising from the endometrium with paraneoplastic retinopathy. *Gynecol Oncol* 1998; 71: 454-457.
- [25] Tsujioka H, Eguchi F, Emoto M, Hachisuga T, Kawarabayashi T, Shirakawa K. Small-cell carcinoma of the endometrium: an immunohistochemical and ultrastructural analysis. *J Obstet Gynaecol Res* 1997; 23: 9-16.
- [26] van Hoesen KH, Hudock JA, Woodruff JM, Suhrland MJ. Small cell neuroendocrine carcinoma of the endometrium. *Int J Gynecol Pathol* 1995; 14: 21-29.
- [27] Huntsman DG, Clement PB, Gilks CB, Scully RE. Small-cell carcinoma of the endometrium: a clinicopathological study of sixteen cases. *Am J Surg Pathol* 1994; 18: 364-375.
- [28] Campo E, Brunier MN, Merino MJ. Small cell carcinoma of the endometrium with associated ocular paraneoplastic syndrome. *Cancer* 1992; 69: 2283-2288.
- [29] Tohya T, Miyazaki K, Katabuchi H, Fujisaki S, Maeyama M. Small cell carcinoma of the endometrium associated with adenosquamous carcinoma: a light and electron microscopic study. *Gynecol Oncol* 1986; 25: 363-371.

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- [30] Manivel C, Wick MR, Sibley RK. Neuroendocrine differentiation in mullerian neoplasms. An immunohistochemical study of a "pure" endometrial small-cell carcinoma and a mixed mullerian tumor containing small-cell carcinoma. *Am J Clin Pathol* 1986; 86: 438-443.
- [31] Paz RA, Frigerio B, Sundblad AS, Eusebi V. Small-cell (oat cell) carcinoma of the endometrium. *Arch Pathol Lab Med* 1985; 109: 270-272.
- [32] Kumar NB. Small cell carcinoma of the endometrium in a 23-year-old woman: light microscopic and ultrastructural study. *Am J Clin Pathol* 1984; 81: 98-101.
- [33] Olson N, Twigg L, Sibley R. Small-cell carcinoma of the endometrium: light microscopic and ultrastructural study of a case. *Cancer* 1982; 50: 760-765.
- [34] Maksem JA, Meiers I, Robboy SJ. A primer of endometrial cytology with histological correlation. *Diagn Cytopathol* 2007; 35: 817-844.
- [35] Norimatsu Y, Kouda H, Kobayashi TK, Shimizu Y, Yanoh K, Tsukayama C, Miyake Y, Ohno E. Utility of liquid-based cytology in endometrial pathology: diagnosis of endometrial carcinoma. *Cytopathology* 2009; 20: 395-402.
- [36] Proca D, Keyhani-Rofagha S, Copeland LJ, Hameed A. Exfoliative cytology of neuroendocrine small cell carcinoma of the endometrium: a report of two cases. *Acta Cytol* 1998; 42: 978-982.
- [37] Ishida M, Iwai M, Yoshida K, Kagotani A, Okabe H. Sebaceous carcinoma associated with Bowen's disease: a case report with emphasis on the pathogenesis of sebaceous carcinoma. *Int J Clin Exp Pathol* 2013; 6: 3029-3032.
- [38] Toriyama A, Ishida M, Amano T, Nakagawa T, Kaku S, Iwai M, Yoshida K, Kagotani A, Takahashi K, Murakami T, Okabe H. Leiomyomatosis peritonealis disseminata coexisting with endometriosis within the same lesions: a case report with review of the literature. *Int J Clin Exp Pathol* 2013; 6: 2949-2954.
- [39] Ishida M, Hodohara K, Yoshida K, Kagotani A, Iwai M, Yoshii M, Okuno K, Horinouchi A, Nakanishi R, Harada A, Yoshida T, Okabe H. Occurrence of anaplastic large cell lymphoma following IgG4-related autoimmune pancreatitis and cholecystitis and diffuse large B-cell lymphoma. *Int J Clin Exp Pathol* 2013; 6: 2560-2568.
- [40] Ishida M, Yoshida K, Kagotani A, Iwai M, Yoshii M, Okuno K, Horinouchi A, Nakanishi R, Harada A, Yoshida T, Okuno T, Hodohara K, Okabe H. Anaplastic lymphoma kinase-positive large B-cell lymphoma: A case report with emphasis on the cytological features of the pleural effusion. *Int J Clin Exp Pathol* 2013; 6: 2631-2635.
- [41] Ishida M, Hodohara K, Yoshii M, Okuno H, Nakanishi R, Horinouchi A, Nakanishi R, Harada A, Iwai M, Yoshida K, Kagotani A, Yoshida T, Okabe H. Methotrexate-related Epstein-Barr virus-associated lymphoproliferative disorder occurring in the gingiva of a patient with rheumatoid arthritis. *Int J Clin Exp Pathol* 2013; 6: 2237-2241.