Small cell carcinoma (SCC) is a distinct clinicopathological 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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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 component. 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 clinico-pathological 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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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.

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.
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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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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.
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