Primary small-cell carcinoma of the endometrium: Clinicopathological study of a case and review of the literature

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Summary

Background: Small-cell carcinomas are almost always primary in the lungs and are highly malignant. These tumors may also occur in the female genital tract. However, primary small-cell carcinoma of the endometrium is extremely rare with very few cases reported in the English literature. This tumor may exhibit evidence of neuroendocrine differentiation and has a high propensity for systemic spread and poor prognosis.

Case: A 55-year-old postmenopausal woman with primary small-cell carcinoma of the endometrium, FIGO stage Ib, underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy and sampling node biopsies of the parametrial spaces, followed by adjuvant combined chemotherapy.

Conclusion: A case of small-cell carcinoma of the endometrium, is reported and its clinical, histological and immunohistochemical features are discussed.

Key words: Small cell; Neuroendocrine; Carcinoma; Endometrial neoplasms.

Introduction

Small-cell (oat cell) carcinomas, are almost always primary in the lungs and are highly malignant [1]. However, similar neoplasms have been reported in various extrapulmonary locations, such as the female genital tract, breast, pancreas, prostate, bowel, stomach, urinary bladder, salivary glands, trachea, larynx and skin [2, 3, 4, 5, 6, 7, 8].

Primary small-cell carcinoma of the endometrium is extremely rare with few cases reported in the English literature [9, 10, 11, 12, 13, 14, 15, 16]. These tumors occur predominantly in postmenopausal women and have poor prognosis, with most of the patients surviving less than one year. Histologically, these tumors are similar to those reported in the lung [2].

Hereby, we present a new case of primary endometrial small cell carcinoma and analyze its clinical, histological and immunohistochemical findings. Also, the literature is reviewed.

Case Report

A 55-year-old gravida 3, para 2, postmenopausal, obese, white woman, previously in excellent health, presented with a two-week history of episodes of abnormal vaginal bleeding (for the previous 14 days). Her last menstrual period was two years before. Her gynaecological history included menarche at age 14 and menstruation every 25 to 30 days, lasting for eight days. Also, she had had a spontaneous first trimester abortion and two caesarian sections. General physical examination was normal. The ectocervix and the vaginal wall were epithelized. On bimanual examination, the clinical estimation of the uterus and ovaries was difficult because of the patient's obesity. Rectal examination revealed no parametrial involvement. Vaginal ultrasound examination showed endometrial thickness of 19.6 mm (Figure 1). Subsequent fractional dilatation and curettage revealed copious amounts of tissue in the endometrial specimen. The distribution of the tumor in the fractional endometrial curretage specimen and its certain histologic and immunohistochemical features rendered the diagnosis of small cell carcinoma of the endometrium with neuroendocrine differentiation.

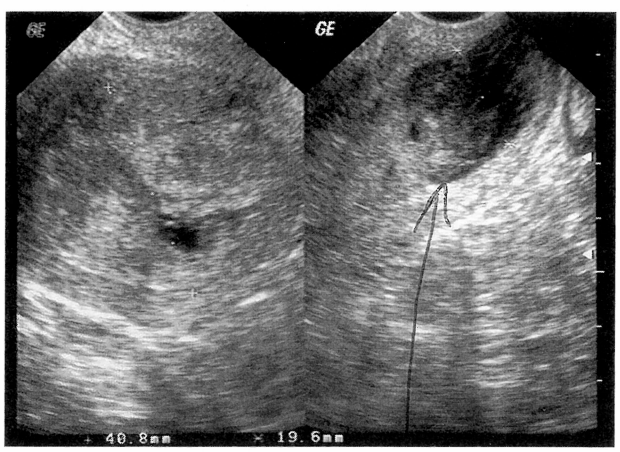

Figure 1. — Vaginal ultrasound scans demonstrating endometrial thickness of 19.6 mm.

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A preoperative chest roentgenogram and computed tomography of the upper and lower abdomen showed no abnormalities. Mammography and clinical examination of the breasts were negative for abnormalities. Preoperative blood count, biochemical tests and serum levels of tumor markers were within normal limits. Exploratory laparotomy revealed the uterus and adnexa to be in normal size. Peritoneal washing was taken for cytological examination. No palpable pelvic or paraortic lymph nodes were found. Total hysterectomy with bilateral salpingo-oophorectomy and sampling node biopsies of the left and right parametrium were carried out. Histopathological examination of the surgical specimens confirmed the presence of primary small-cell carcinoma of the endometrium. The stained cytologic smears of the peritoneal washing were negative for malignancy.

The patient received routine postoperative care, made an unremarkable recovery and was discharged seven days later. She was assigned to FIGO stage Ib and six courses of adjuvant chemotherapy (carboplatin and etoposide) were administrated.

Material and Methods

The surgical specimen was fixed in 10% formalin. Representative samples were embedded in paraffin and 4 μm thick sections were stained with haematoxylin and eosin. Immonohistochemical analysis was performed using an indirect immunoperoxidase technique with dianobenzidine (DAB) as chromogen. The following primary antibodies were used: pan-keratin (clone AE1/AE3, 1:50 dilution, Daco), cytokeratin 7 (clone OV-TL 12/30, 1:50 dilution, Dako), cytokeratin 8 (clone 35, H11, 1:100 dilution, Dako), cytokeratin 20 (clone IT-KS20.8, prediluted, Biogenex), epithelial membrane antigen/EMA (clone E29, 1:100 dilution, Daco), epithelial antigen (clone Ber-EP4, 1:50 dilution, Daco), carcinoembryonic antigen/CEA (clone II-7, 1:200 dilution, Daco), chromogranin A (clone LK2H10, 1:100 dilution, Biogenex), synaptophysin (clone SYPO2, prediluted, Neomarkers), neuron specific enolase (NSE) (polyclonal, 1:100 dilution, Biogenex), vimentin (clone V9, 1:100 dilution, Daco), S-100 protein (polyclonal, 1:1,200 dilution, Daco) and Leu-7 (clone HNK-1, 1:10 dilution, Becton Dickinson).

Pathology

Gross Appearance

The uterus measured 8 × 5 × 3 cm. The ectocervix and the endocervical mucosa were smooth and glistening. The endometrial cavity was filled by an exophytic polypoid mass, protruding from the fundus. The endometrial polyp measured 2.5 cm in its greater diameter. Its cut surface was gray-white and its consistency friable. The thickness of the myometrium in the position of the polypoid mass was 1.6 cm.

The fallopian tubes and ovaries were unremarkable. The biopsies from the right parametrium revealed one grossly normal lymph node measuring 0.3 cm and from the left parametrium one grossly normal lymph node measuring 2.5 cm. Both lymph nodes had mottled gray-white cut surfaces.

Light microscopic findings

Haematoxylin and eosin stained sections of the initial endometrial curettage specimens showed invasive neoplasm that was diagnostic of small cell carcinoma of the endometrium. The tumor was composed of solid and trabecular sheets of small, relatively uniform cells interspersed by a fibrous, focally oedematous stroma (Figures 2 and 3). The cells had scant, lightly eosinophilic cytoplasm and hyperchromatic round nuclei with indistinct nucleoli. Mitotic figures were numerous.

At autopsy, tumor remnants of small cell carcinoma were found in the described polypoid endometrial mass corresponding to the position of the fundus uteri. The underlying myometrium was infiltrated in depth of 0.6 cm, while the whole thickness of myometrium at this position was 1.6 cm (myome-

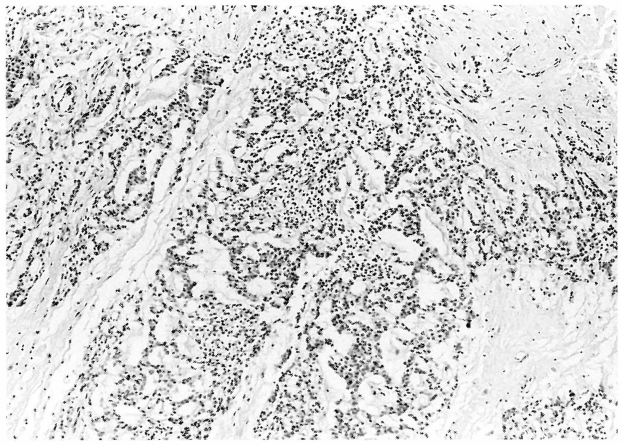

Figure 2. — Cords and trabeculae of small, uniform neoplastic cells (H&E × 100).

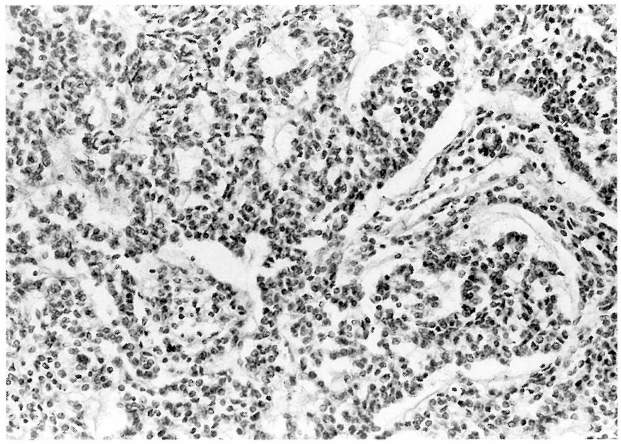

Figure 3. — The same as Figure 1 (H&E × 200).

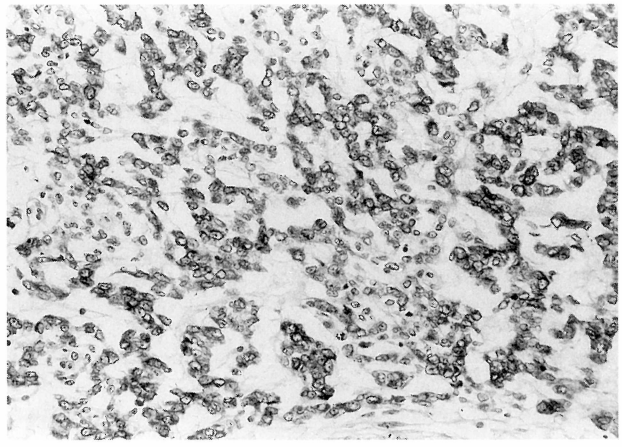

Figure 4. — Expression of cytokeratin 7 in tumor cells (× 200).

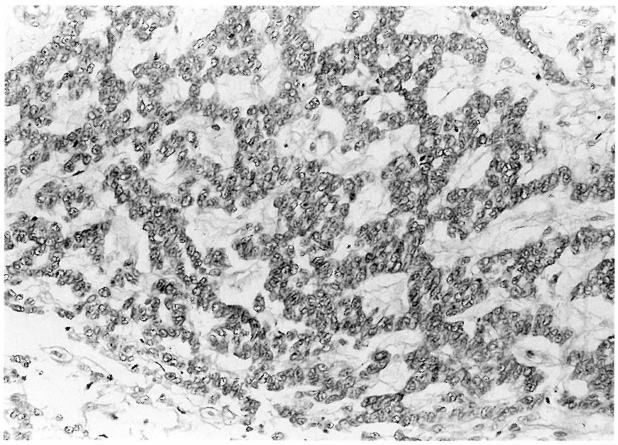

Figure 5. — Expression of cytokeratin 8 in tumor cells (× 200).

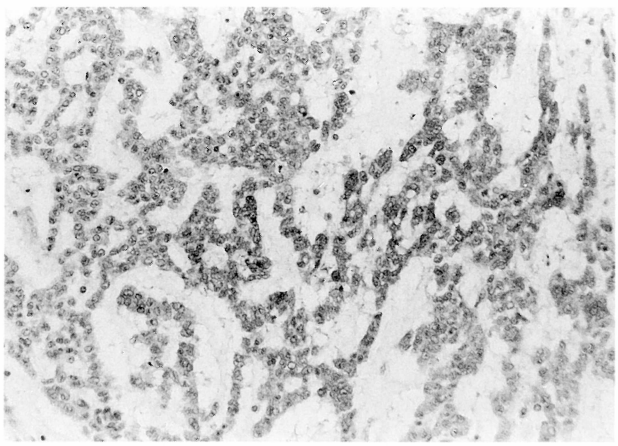

Figure 6. — Focal positivity of tumor cells for NSE (× 200).

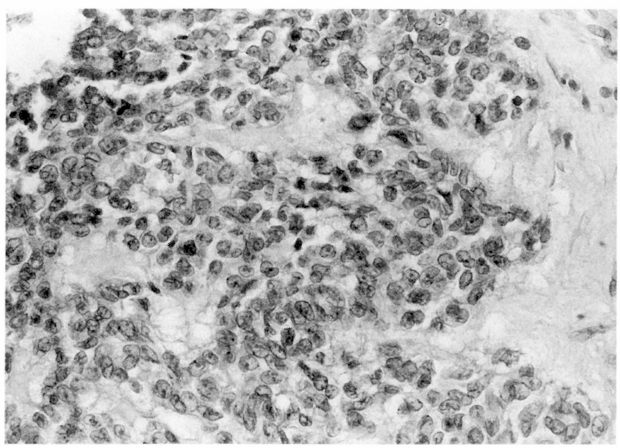

Figure 7. — Focal positivity of tumor cells for Leu-7 (× 400).

trial invasion less than 50%). No glandular or squamous differentiation was present. There was no capillary-like space involvement. The rest of the endometrium was irregularly proliferative.

Multiple sections of the ectocervix and endocervical canal were unremarkable for tumor involvement. Adnexal structures were normal. No metastatic tumor was found in the pelvic lymph nodes.

Immunohistochemical findings

Immunohistochemically, the tumor cells were strongly and diffusely positive for pan-keratin AE1/AE3, cytokeratin 7 (Figure 4) and cytokeratin 8 (Figure 5). These cells were focally positive for NSE (Figure 6) and Leu-7 (Figure 7), while they stained negative for chromographin, cynaptophysin, EMA, CEA, Ber-EP4, S-100 protein, cytokeratin 20 and vimentin.

Discussion

Primary small-cell carcinomas of the female genital tract are very rare and more commonly seen in the uterine cervix [17] and ovary [2]. In the cervix, variable proportions of these tumors exhibit evidence of neuroendocrine differentiation [18]. In the ovary, the most common type of small-cell carcinoma typically occurs in young women, is associated with hypercalcemia in two-thirds of the cases, and lacks neuroendocrine features [18]. The other, a rare type of ovarian small-cell carcinoma, occurs predominantly in postmenopausal women, is not associated with hypercalcemia and resembles pulmonary small-cell carcinomas. Small-cell carcinoma arising elsewere in the female genital tract, including the vagina and the endometrium are very rare [18].

The histogenesis of neuroendocrine tumors of the endometrium remains uncertain [2]. One theory suggests that small-cell carcinoma of the endometrium stems from neuroendocrine cells of normal endometrium [19]. This hypothesis is consistent with studies that have documented neuroendocrine cells within normal endometrial glands [19, 20] and more commonly within well-differentiated endometrial adenocarcinomas [2, 10, 20]. An alternative theory is neuroendocrine metaplasia of the müllerian epithelium [2, 19].

The clinical presentation of endometrial small-cell carcinoma is similar to that of the other forms of endometrial adenocarcinoma [2] and includes menorrhagia, metrorrhagia, postmenopausal bleeding, lower abdominal pain, abdominal distention and abnormal vaginal cytology [2, 18]. In addition, in some cases small-cell carcinoma of the endometrium is associated with paraneoplastic retinopathy [2, 16, 21]. This association suggests that small-cell carcinoma of the genital tract may be a subset of tumors related to paraneoplasmatic syndrome in the absence of metastatic disease in the eye or brain [2]. However, our patient did not complain about any visual disturbance and her only symptom was postmenopausal bleeding.

A classification system for endocrine tumors of the cervix has recently been proposed by a workshop sponsored by the College of American Pathologists and the National Cancer Institute [22]. The neoplasm described here histopathologically consisted of small cells with scant cytoplasm and hyperchromatic nuclei. These cells were arranged in nests and cords. These findings fit perfectly within the category of small (oat) cell carcinoma that is usually seen in the lung and occasionally in other epithelial organs. Tissue sections in our case stained strongly and diffusely with AE1/AE3 and cytokeratins 7 and 8. They showed focal positive staining for the neuroendocrine

screening markers Leu-7 and NSE. The antigen NSE is found in neurons, normal cells in the neuroendocrine system, and in tumors with neuroendocrine differentiation. It has also been demonstrated in non-neuronal normal and neoplastic tissues and is thus not a specific marker for neuroendocrine differentiation. However, it is a useful screening tool in detecting cells with neuroendocrine features [19]. In our study, stainings for chromographin, synaptophysin, EMA, CEA, Bcr-EP4, S-100 protein, cytokeratin 20 and vimentin were negative. In a review of the literature, staining for cytokeratin of small-cell carcinoma of the endometrium was found in 80 to 100% of the studied cases [18, 23], staining for NSE in 82 to 100% [16, 21] and staining for chromographin in 11 to 33% [18, 23]. Other markers that have been found less commonly include Leu-7 [23], synaptophysin [23], bombesin [23], protein S-100 [23], insulin [2], serotonin [2] and beta-endorphin [23]. Co-expression of cytokeratin and vimentin is common in carcinomas. In the study by Abeler *et al.*, vimentin co-expressed with cytokeratin in 57% of the cases [23]. In another study, vimentin immunoreactivity was found in 58% of endometrial carcinomas primary fixed in buffered formalin and in 79% of alcohol-fixed specimens [24].

The differential diagnosis of primary small-cell carcinoma of the endometrium requires exclusion of metastases from other sites with a focal or diffuse malignant small cell component and particularly the lung and the cervix. In the case we present, there was no evidence of disease in the lung or any other organ at any time during the patient's life. Also, an obvious endometrial polypoid mass was found at the fundus uteri with histological and immunohistochemical features of small-cell neuroendocrine carcinoma of the endometrium. Multiple sections of the ectocervix and endocervical canal from the hysterectomy specimens revealed no involvement of the cervix. The adnexa structures were unremarkable as well. Also, the mammography and the clinical examination of the breasts showed no abnormalities. These findings suggested that the primary site of the tumor was the endometrium. The differential diagnosis of small-cell carcinoma of the endometrium includes malignant lymphoma and leukemia [25], endometrial stromal sarcoma, rhabdomyosarcoma, small-cell nonkeratinizing squamous carcinoma [15], adenocarcinoma with neuroendocrine features, primitive neuroectodermal tumors [26] and metastatic breast carcinoma [19]. However, each tumor has certain histologic features and characteristic immunohistochemical features that are useful in making the distinction [19].

Small-cell carcinoma of the endometrium is frequently diagnosed at an advanced stage and is associated with systemic spread and a poor prognosis [18]. For the treatment of small-cell carcinoma of the endometrium thorough intraoperative staging should be performed at the time of hysterectomy if the disease has been established on a curettage specimen [18]. In patients with low-stage neoplasia adjuvant chemotherapy is needed because of its aggressive behavior, while in patients with a higher stage disease the treatment should include debulking of the tumor combined with chemotherapy, radiation therapy or both [18]. The treatment in the patient we present consisted of total hysterectomy with bilateral salpingo-oophorectomy and sampling node biopsies of the left and right parametrium. The patient was assigned to FIGO Stage Ib and postoperative combined chemotherapy of carboplatin and etoposide was given because of the described aggressive behavior of small-cell carcinoma of the endometrium.

In conclusion, we presented a case of small-cell carcinoma of the endometrium, a rare highly malignant tumor and discussed its clinical, histological and immunohistochemical features.

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