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TEACHING CASES

Primary pure large-cell neuroendocrine carcinoma of the ovary

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Abstract

We report a case of a 73-year-old female with a rare simultaneous occurrence of three tumors: ovarian carcinoma, endometrial carcinoma, and breast carcinoma. The ovarian tumor was a primary pure large-cell neuroendocrine carcinoma. Grossly, the left ovary was enlarged by a solid tumor that measured 9 × 7 × 7 cm. Histologically, the tumor consisted of large cells with irregular hyperchromatic nuclei and a moderate amount of eosinophilic cytoplasm. In some areas, the tumor cells were arranged in solid sheets; however, the predominant pattern was cribriform and solid-alveolar, with palisaded tumor cells located peripherally. The tumor cells showed multiple mitotic figures (up to 43 mitoses/10 HPF). Large areas of tumor necrosis were found. Immunohistochemically, the tumor cells were positive for EMA, synaptophysin, chromogranin, CD56, and CEA. Cytokeratin 20 was positive focally. Primary large-cell neuroendocrine carcinoma of the ovary is a rare tumor. To the best of our knowledge, only 4 cases of a pure tumor of this type have been reported to date.

Keywords: Ovary; Neuroendocrine carcinoma; Large cell; Tumor triplicity

Introduction

Primary large-cell neuroendocrine carcinoma of the ovary (ovarian non-small cell neuroendocrine carcinoma) is a rare entity that was recently included in the latest WHO classification of ovarian tumors [21]. It has been shown that surface epithelial-stromal tumors of the ovary and teratomas may contain a small proportion of neuroendocrine cells [9,11,15,22]. Therefore, it is not surprising that composite tumors of the ovary consisting of a surface epithelial-stromal tumor and/or a germ cell tumor associated with a neuroendocrine tumor occur. The neuroendocrine component of these mixed tumors is composed of carcinoid, small cell carcinoma of the pulmonary type, and large-cell neuroendocrine carcinoma [3,10,20]. We found that only 24 cases of ovarian composite tumor consisting of large-cell neuroendocrine carcinoma associated with surface epithelial-stromal tumor and/or teratoma have been reported to date [1,4–6,8,13,14,17,23]. In addition, four cases of primary large-cell neuroendocrine carcinoma of the ovary without any other associated component have been described [2,16,23,24]. We report an additional case of primary pure large-cell neuroendocrine carcinoma of the ovary that occurred in a 73-year-old female.

Case report

A 73-year-old female was admitted to our hospital for dysartria and difficulties in verbal expression. Brain

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MRI showed a metastatic CNS disease in the left frontal lobe and smaller foci in the cerebellum. Her past medical history revealed treatment for breast cancer 22 years ago. The left front lobe CNS metastasis was removed surgically, and the smaller cerebellar metastases were treated radiosurgically using the Gamma Knife. The CNS metastasis was histologically identified as a neuroendocrine carcinoma. To locate the primary tumor, the gastrointestinal tract and lungs were examined, with negative results. The patient was referred to the Oncogynecological Center of our hospital. An ultrasound examination showed a highly vascularized solid tumor in the left uterine adnexa, an irregular polypose endometrium of suspect nature, and another highly vascularized tumor above the left kidney. Under ultrasound guidance, a tru-cut biopsy of the tumor in the left ovary and a hysteroscopical biopsy of the endometrium were performed. Based on a histological analysis, a primary ovarian tumor with CNS metastasis and an additional tumor in the endometrium were considered. Tumor marker values were as follows: NSE 23 μg/l, CA 125 94 kIU/l, CA 19-9 133 kIU/l. The patient was in a good performance status, and a debulking surgery consisting of abdominal hysterectomy with bilateral adnexectomy, left-sided nephrectomy, omentectomy, and mesenterial metastasis resection was performed. No macroscopic residual tumor was left in the abdominal cavity. The final histological analysis revealed a rare simultaneous occurrence of three tumors in the patient: breast carcinoma (FIGO Stage I, first diagnosed in 1985, in complete remission), endometrial carcinoma (FIGO Stage IIA), and ovarian carcinoma (FIGO Stage IV) with metastatic spread to the mesenterium, the left renal capsule, and the CNS. The patient received adjuvant chemotherapy with paclitaxel and carboplatinum. Two months later, during a regular follow-up examination, a CNS recurrence was diagnosed that was presumably due to the inability of chemotherapy agents to cross the hematoencephalic barrier. The newly discovered metastatic foci in the frontal lobe were successfully treated again using Gamma Knife. At present, the patient is in a good status (PS 0), with no signs of tumor relapse 1 year after the first diagnosis of metastasized ovarian cancer.

Materials and methods

This study comprised the following specimens: a tru-cut biopsy of the tumor in the left ovary, hysteroscopical biopsy of the endometrium, hysterectomy with bilateral adnexectomy, left nephrectomy, omentectomy, splenectomy, and resected mesenterial metastasis. In addition, slides from the resected brain metastasis examined at another institution were reviewed. Sections from formalin-fixed, paraffin-embedded tissue blocks were stained with hematoxylin–eosin. Selected sections were examined immunohistochemically using the avidin–biotin-complex method with antibodies directed against the following antigens: vimentin (1:300, Bio-Genex, San Ramon, CA, USA), EMA (1:100, Dako, Glostrup, Denmark), TTF1 ( ), α-inhibin (1:25, Dako), S-100 protein (1:400, Dako), α-actin (1:100, Dako), cytokeratin 7 (1:25, Dako), cytokeratin 20 (1:50, Dako), CEA (1:100, Dako), CD56 (1:50, Novocastra, Newcastle, UK), synaptophysin (1:25, Dako), chromogranin A (1:50, Dako), estrogen receptor (1:100, Dako), progesterone receptor (1:100, Dako), serotonin (1:10, Dako), and somatostatin (1:200, Dako). Monoclonal antibody MIB-1 (1:50, Dako) was used for assessing proliferative activity.

Results

The composition of the material examined was as follows: a tru-cut biopsy of the tumor in the left ovary, a hysteroscopical biopsy of the endometrium, specimens obtained at hysterectomy with bilateral salpingo-oophorectomy, as well as material from omentum, spleen, left kidney with adrenal gland and perirenal fatty tissue with metastasis, and metastasis resected from the mesenterium. The slides from the brain metastasis examined at another institution were reviewed.

Grossly, the uterine corpus measured $50 \times 45 \times 30$ mm. The myometrium was up to 15 mm thick. In cross section, the endometrium consisted of white friable tumor tissue up to 4 mm in thickness. The uterine cervix, right tuba, and right ovary showed no apparent changes. The left ovary consisted of a lobulated tumor $95 \times 70 \times 68$ mm. The serosa was intact. In cross section, the tumor was grayish-white and solid with focal hemorrhages. The left tuba was normal. The omentectomy specimen was normal. The spleen showed a focal rupture of the capsula. The mesenterial metastasis consisted of fatty tissue $25 \times 20 \times 15$ mm with white tumor tissue. The left kidney was normal, but in the renal capsule, there was metastasis ($80 \times 70 \times 40$ mm).

Histologically, the tumor of the uterus was endometroid adenocarcinoma with focal squamous differentiation. The tumor had architectural grade 2, but was upgraded to grade 3 because of marked nuclear atypia. The tumor showed only focal myometrial invasion (maximum depth of invasion 1 mm); however, evidence of tumor spreading into the mucosa of the uterine cervix was found (pT2a). Immunohistochemically, the tumor cells were focally positive for estrogen and progesterone receptor, whereas neuroendocrine markers including synaptophysin, chromogranin, and CD56 were negative.