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Letter to the Editor

Anti-NMDA receptor encephalitis due to large-cell neuroendocrine carcinoma of the uterus☆

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ABSTRACT

A 44-year-old woman presented with a large-cell neuroendocrine carcinoma and uterine endometrioid carcinoma with anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis. Following the diagnosis of uterine cancer, the patient suddenly developed psychosis with abnormal behaviors, delusions, irritability, and forgetfulness. The cerebrospinal fluid tested positive for anti-NMDAR antibodies (encoding the NR1 subunit). The patient was diagnosed with paraneoplastic limbic encephalitis due to uterine cancer. Histology of multiple abdominal metastatic samples revealed a neuroendocrine tumor. Her consciousness improved temporarily after tumor resection and comprehensive immunomodulatory therapy. On day 104 after admission, the patient died of multiple organ failure. The autopsy revealed a perivascular infiltration of inflammatory cells in the amygdala and NMDAR-positive cells in the primary uterine cancer. Our findings demonstrated that neuroendocrine tumors can induce anti-NMDAR encephalitis, which is consistent with three previous reports. A comprehensive treatment with resection of the carcinoma, immunoglobulins, and plasma exchange can induce a partial improvement of the symptoms.

Dear Editor

1. Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is a paraneoplastic syndrome with neuropsychiatric disturbances that usually manifests as a consciousness disturbance, behavioral changes, psychosis, and convulsions [1]. Most of the reported cases are associated with neoplasms, mainly ovarian teratomas [2]. Herein, we report on a patient with a large cell neuroendocrine tumor (LCNEC) and endometrioid carcinoma of the uterus who developed anti-NMDAR encephalitis along with pathological assessments.

2. Case report

Our case was of a 44-year-old woman. Twelve days before admission in our hospital, she was diagnosed with uterine cancer at another hospital. The gynecological examinations showed atypical glandular cells on endocervical cytology. Pelvic magnetic resonance imaging (MRI) showed uterine cancer (72 × 31 mm in sagittal view) (Fig. 1A), invasion into the cervix of the uterus, metastasis to the bilateral ovaries, and lymph node swelling in the left external iliac node. A positron emission tomography-computed tomography scan indicated no metastasis in other organs. We diagnosed FIGO stage IIIC1 uterine cancer. Five days before admission, she suddenly developed psychosis with abnormal behaviors, delusions, irritability, and forgetfulness, and was then transferred to our hospital. During the first examination, she was semicomatose (E4V1M1 on the Glasgow coma scale), with Cheyne-Stokes respiration and a continuous high fever. We observed involuntary movements of the mouth and tongue, compatible with oral automatism, and restricted eye movements in all directions.

Brain MRI revealed no abnormal findings. Biochemical examination of the peripheral blood indicated increased levels of CA125: 51 U/ml (normal ≤ 35 U/ml). A cytobiochemical examination of the cerebrospinal fluid (CSF) revealed a cell count of 12/μl (≤ 5/μl), a normal level of protein 25 mg/dl (≤ 45 mg/dl), and a normal level of glucose 60 mg/dl (≤ 75 mg/dl). The CSF was positive for anti-NMDAR antibody (titer 1:400), the antigen being extracellular domains of the NR1 subunit of the receptor (anti-NMDA receptor antibodies, EUROIMMUN, Luebeck, Germany). We additionally assessed antibodies related to paraneoplastic syndrome such as anti-Hu, Yo, Ri, GAD65, Ma2/Ta, Amphihisin, Titin, SOX1 antibodies in peripheral blood, using a commercial lineimmunoblot assay, EUROLineScan (Euroimmun, Luebeck, Germany). All results were negative. Thus, we diagnosed anti-NMDAR encephalitis due to uterine cancer.

On day 4 after admission, she underwent an operation for total resection of the tumor and the metastasis to the greater omentum. The pathological findings revealed mixed carcinoma of the LCNEC and endometrioid adenocarcinoma (grade 3) (Fig. 1B–C). Immunohistochemical staining showed positivity for chromatin A, synaptophysin, and CD56 in the metastatic and disseminated carcinoma in the omentum and left and right adnexa (Fig. 1D–F). After surgery, she remained comatose. Thus, we additionally initiated immunomodulation therapies of plasma exchanges (three time in

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Abbreviations: LCNEC, large cell neuroendocrine carcinoma; NMDAR, *N*-methyl-D-aspartate receptor; CSF, cerebrospinal fluid

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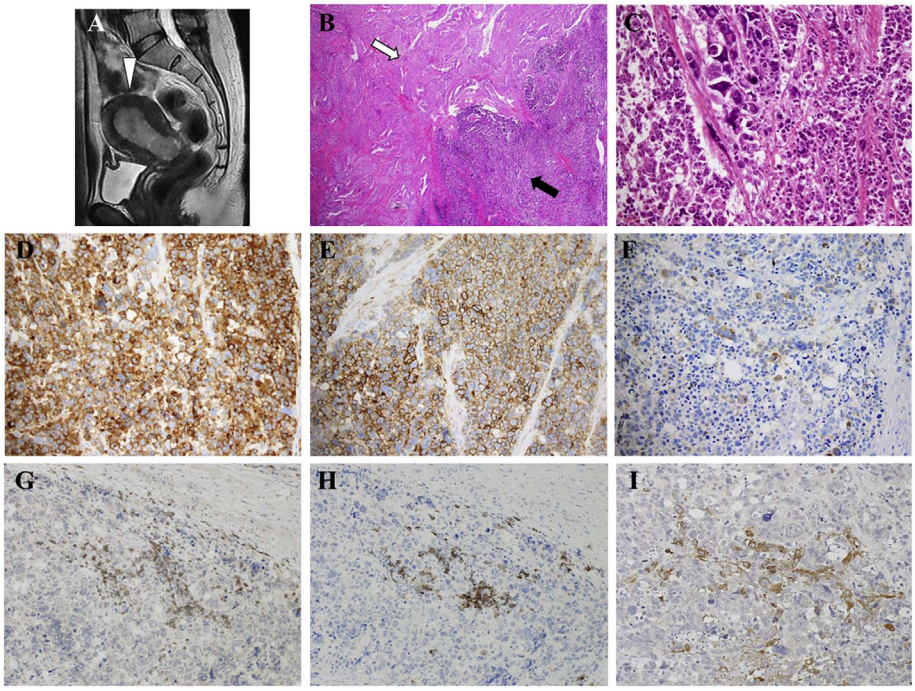

Fig. 1. Pelvic MRI findings and results of pathology in uterus carcinoma
(A) The pelvic MRI, sagittal view, revealed a 72 × 31 mm uterine cancer (white triangle). (B) Microscopic findings for the removed tumor on hematoxylin and eosin staining; a trabecular pattern of tumor cells (white arrow), and a poorly differentiated neuroendocrine tumor (black arrow). (C) The neuroendocrine tumor consists of large size anaplastic cells with cell necrosis. Immunohistochemistry shows the cells positively stained for specific markers for neuroendocrine tissue, synaptophysin (D), CD56 (E), and chromogranin A (F). Each protein is well known to be presented in neuroendocrine cells. The pathological diagnosis was mixed carcinoma of large cell neuroendocrine carcinoma and endometrioid adenocarcinoma. Another immunohistochemistry reveals the presence of lymphocytic infiltration in the neuroendocrine cells, demonstrated by antibodies to CD3 (T cells) (G) and CD20 (B cells) (H). (I) The cells expressing NMDAR1 were detected by immunohistochemistry using a rabbit monoclonal antibody to NMDAR1 (clone EOR2480Y, Abcam, Cambridge, UK) in the primary uterine cancer. Original magnification, × 20 (B), and × 400 (C–I).

a week) and 5 days of intravenous immunoglobulin infusion therapy (400 mg/kg/day). On day 7, she was on mechanical ventilation management due to an intractable seizure, ameliorated by using continuous infusion of thiopental, levetiracetam (1500 mg/day), and phenobarbital (140 mg/day). One month after initiating treatment, her consciousness improved to E4V4M6; she began communicating using simple gestures. We then started chemotherapy with paclitaxel 90 mg and carboplatin 240 mg for the uterine cancer and metastases from day 68.

Although she seemed to be maintaining her stable condition, on day 104, she died of multiple organ failure. After obtaining informed consent from family members, an autopsy was performed. The pathological findings at autopsy showed 1300 g of brain, carcinomatous peritonitis, and bilateral hydronephrosis due to invasion by the tumor and bone metastasis to the lumbar bone marrow and pneumonia.

The histology of the abdominal multiple metastases revealed atypical round cells of neuroendocrine tumors along with positivity of synaptophysin, CD56, and chromogranin A. In the brain, there was perivascular infiltration of inflammatory cells in the amygdala. The primary uterine cancer were stained by both CD3 and CD20 antibodies, which indicate the inflammatory infiltrates of T cells and B cells, commonly seen in anti-NMDAR encephalitis associated with ovarian teratoma (Fig. 1G and H) [2]. NMDAR-positive cells were also detected in the primary uterine cancer by immunohistochemistry using an anti-NMDAR antibody (Fig. 1G).

3. Discussion

LCNEC arising from the uterine endometrium is extremely rare and represents < 1% of all primary endometrial carcinomas [3]. In most of the cases, it is derived from the lungs. WHO classification of pulmonary tumors defines LCNEC as a large cell carcinoma with neuroendocrine tumor morphology [4]. Any poorly differentiated neuroendocrine carcinoma has a severe prognosis. The LCNEC in our case was derived from the uterine endometrium and associated with anti-NMDAR encephalitis. Anti-NMDAR encephalitis commonly arises from ovarian teratoma [1]. Thus, our case had two rarities of (i) LCNEC arising from the uterus endometrium, and (ii) anti-NMDAR encephalitis associated with LCNEC.

Three cases have been previously reported as neuroendocrine carcinoma and anti-NMDAR encephalitis (Supplementary Table 1) [5–7]. All four cases including ours involved different types of carcinoma including a sarcoma from the uterus, a pancreatic tumor, a hepatocellular carcinoma, and an endometrioid adenocarcinoma from the uterus. All cases were complicated by psychosis or symptoms related to the central nervous system at onset. In three out of the four cases, tumors expressing NMDAR were detected pathologically by a GluR1 antibody encoding the NR1 subunit that binds glycines, meaning that various types of cancers can produce NMDAR on the cell surface.

Each patient's outcome depended on the degree of cellular differentiation. Three cases with poorly differentiated cells had poor outcomes, but two of them had temporarily good outcomes after immunomediated therapies. The definitive therapies for patients with neuroendocrine carcinoma with anti-NMDAR encephalitis are controversial, because the number of the reported patients is small. Some patients manifested temporary good responses after immunomediated therapies and tumor resection. LCNEC with an endometrial tumor is usually treated by surgical resection, radiation, and chemotherapy [4]; unfortunately our case had only partial responses to chemotherapy.

In conclusion, anti-NMDAR encephalitis can emerge from various types of tumors. If the patients do not complicate with ovarian teratoma, whole-body screening for malignancy after 45-year-old is warranted for patients with anti-NMDA antibody encephalitis.

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