INTERNAL MEDICINE

□ CASE REPORT □

Paraneoplastic Limbic Encephalitis in a Human Epidermal Growth Factor Receptor-2-positive Gastric Cancer Patient Treated with Trastuzumab-combined Chemotherapy: A Case Report and Literature Review

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Abstract

Paraneoplastic neurological syndromes (PNSs) are rare nervous system dysfunctions in cancer patients, which are primarily observed with small-cell lung cancer, gynecological cancer, and thymoma. We herein present an uncommon case of PNS in an anti-Hu antibody-positive patient with human epidermal growth factor receptor (HER)-2-positive gastric cancer (GC), who developed limbic encephalitis and a worsening cognitive function. Trastuzumab-combined chemotherapy was initiated and appeared to be partially effective for controlling the neurological symptoms and tumor volume. Chemotherapy failure eventually led to uncontrollable neurological symptoms. This is the first case demonstrating that trastuzumab-combined chemotherapy may be effective for controlling neurological symptoms of PNS in HER2-positive GC patients.

Key words: gastric cancer, trastuzumab, HER-2, paraneoplastic limbic encephalitis, anti-Hu antibody

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Introduction

Paraneoplastic neurological syndromes (PNSs) are rare neurological disorders of unknown cause that are often observed in association with cancer (1). The identification of several antibodies against neural antigens in primary tumors (onconeural antibodies) has suggested that the development of PNSs is immune-mediated. As specific onconeural antibodies are associated with several different cancers and neurological syndromes, the detection of onconeural antibodies may contribute to the identification of the primary site of cancers (1). However, the scientific literature on PNSs in gastric cancer (GC) is scarce; hence, detailed information on specific onconeural antibodies and neurological syndromes associated with GC remains unknown. We herein report the rare case of a patient with human epidermal growth factor receptor (HER)-2-positive GC who developed limbic encephalitis and was positive for anti-Hu antibodies and provide a literature review of PNSs accompanying GC. Our case is the first report to demonstrate that trastuzumab-combined chemotherapy may contribute to the management of PNS-associated neurological symptoms in HER2-positive GC patients.

Case Report

A 71-year-old Japanese man had no history of dementia and had been healthy until approximately 2 weeks prior to his first visit at a community hospital. However, his family

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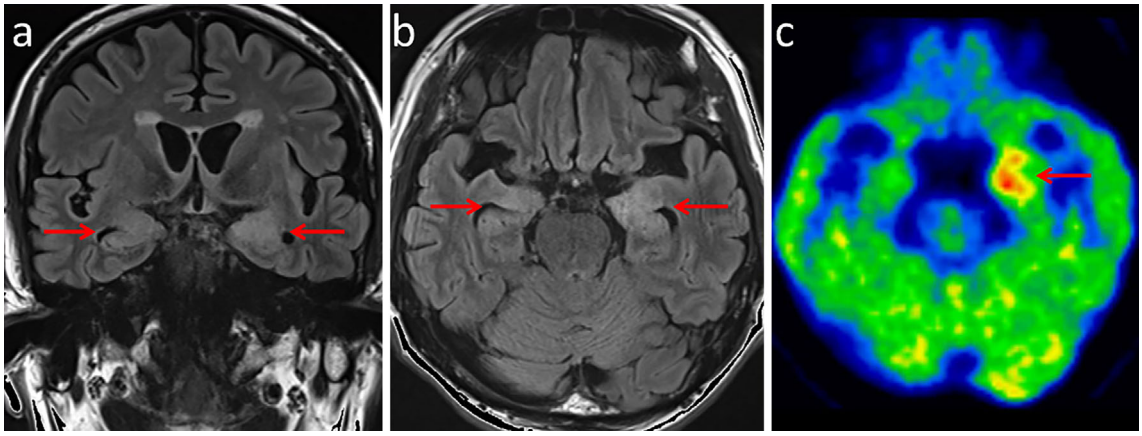

Figure 1. **a, b: MRI (T2-weighted FLAIR images) of the head revealed a high intensity signal in the bilateral limbic system. c: PET/CT of the brain showed increased FDG avidity in the left mesial temporal region (SUVmax, 13.2). CT: computed tomography, FDG: ^{18}F-fluorodeoxyglucose, FLAIR: fluid-attenuated inversion recovery, MRI: magnetic resonance imaging, PET: positron emission tomography**

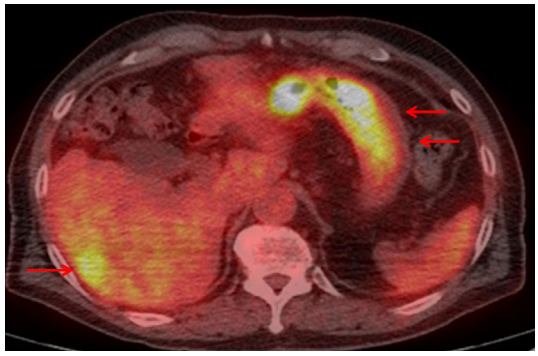

Figure 2. **PET/CT showed a tumor-specific uptake in the liver (SUVmax, 5.5) and stomach (SUVmax, 6.9). CT: computed tomography, FDG: ^{18}F-fluorodeoxyglucose, PET: positron emission tomography, SUV: standardized uptake value**

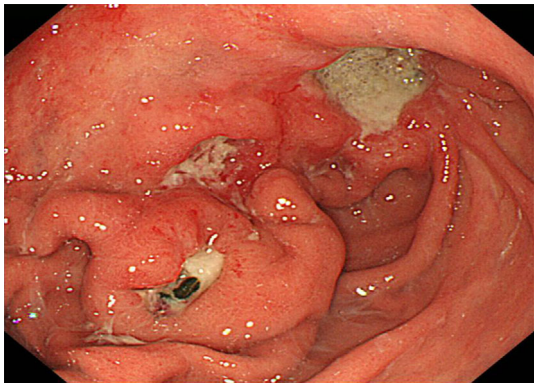

Figure 3. **EGD revealed the presence of multiple type-5 tumors in the body of the stomach. EGD: esophagogastroduodenoscopy**

had consulted the hospital because of a rapid deterioration in cognitive function, general malaise, and an attack of unconsciousness. Magnetic resonance imaging (MRI; T2-weighted fluid-attenuated inversion-recovery images) of the brain revealed hyperintensity in the bilateral mesial temporal regions(Fig. 1a, b). Therefore, he was referred to our hospital for further assessment and treatment.

A neurological examination performed at our hospital showed cognitive dysfunction; in particular, we observed disorientation, acalculia, and memory disturbance [Minimal Mental State Examination score (MMSE) 18/30; Wechsler Memory Scale-Revised (WMS-R): verbal memory, 69; visual memory, 70; general memory, 67; attention/concentration, 93; and delayed recall, 59]. Frequent complex partial seizures were observed, resulting in unresponsiveness. A routine electroencephalography (EEG) examination revealed frequent EEG seizure patterns originating from the left temporal area.

Laboratory tests showed normal levels of vitamin B_{12}, folic acid, antinuclear antibody, and thyroid hormones. An elevated erythrocyte sedimentation rate (26 mm/h) and elevated levels of carcinoembryonic antigen (5.2 ng/mL) were detected. A cerebrospinal fluid analysis revealed a white blood cell count of 10/μL and a protein level of 48.4 mg/dL, without malignant cells.

Positron emission tomography (PET)/computed tomography (CT) of the brain showed increased ^{18}F-fluorodeoxyglucose (FDG) avidity in the left mesial temporal region [maximum standardized uptake value (SUVmax), 13.2; Fig. 1c]. CT of the abdomen showed several low-density areas in the liver. Suspecting PNS, we performed PET/CT in order to detect the primary site of the cancer; stomach and liver lesions showed increased FDG avidity (SUVmax liver, 5.5; SUVmax stomach, 6.9; Fig. 2).

Esophagogastroduodenoscopy revealed multiple ulcerative lesions with giant folds in the body of the stomach (Fig. 3). The lesions were characterized as Type V according to the Borrmann classification and exhibited atypical macroscopic features similar to primary gastric adenocarcinoma. However, a histological examination of biopsy specimens from

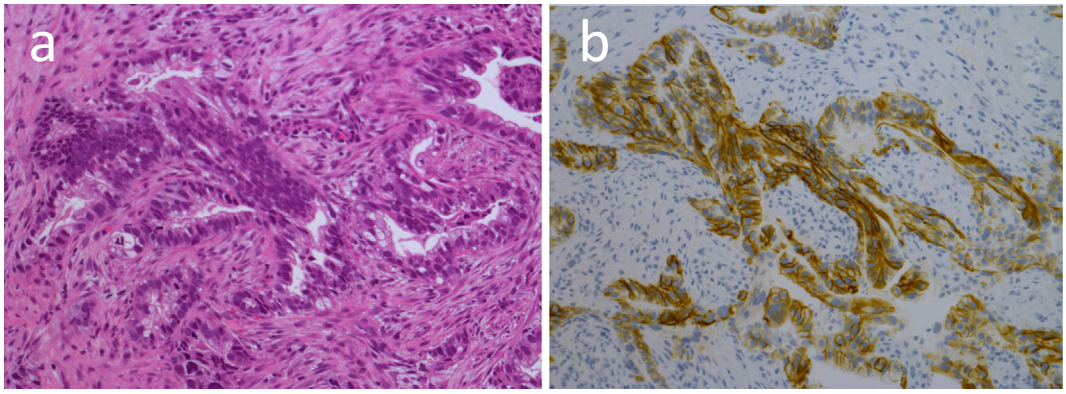

Figure 4. **(a) Hematoxylin and Eosin staining. (b) An immunohistochemical analysis showing strong staining for HER2. HER2: human epidermal growth factor receptor-2**

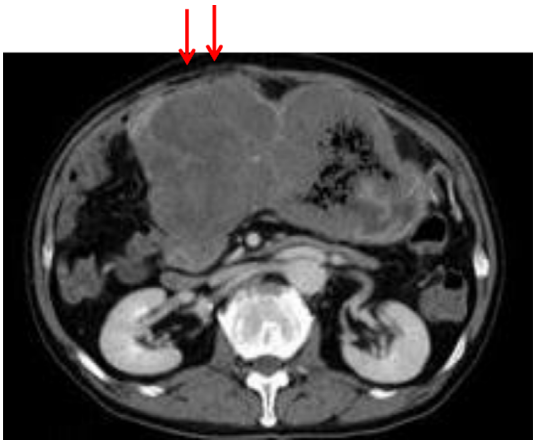

Figure 5. **CT of the abdomen showed exuberant growth of the gastric cancer. CT: computed tomography**

each lesion divulged the presence of well-differentiated adenocarcinoma showing 3^{+} HER2 expression, as assessed by immunohistochemistry (Fig. 4). Moreover, in PET/CT, a FDG uptake could not be recognized in any organs other than the brain, stomach, and liver. We therefore speculated that the stomach was most likely the primary cancer site.

According to these results, serum onconeural antibodies (anti-Titlin, anti-SOX1, anti-Hu, anti-Yo, anti-Ma2/Ta, anti-CV2, and anti-Amp antibodies) were tested, and the presence of anti-Hu antibody was identified; however, other antibodies against synaptic or neuronal cell-surface antigens (NMDA and GABA) were not tested. Under the provision of the available diagnostic criteria (1), the patient was diagnosed with definite PNS with HER2-positive stage IV gastric adenocarcinoma (cT3N0M1).

To treat the cancer and relieve the neurological symptoms, capecitabine, cisplatin, and trastuzumab (XP+HER) therapy was initiated. In conjunction with chemotherapy, two courses of pulse corticosteroid therapy were administered. However, both failed to improve the symptoms (MMSE, 18/30). After the first course of chemotherapy, cisplatin-related acute kidney dysfunction progressed, and we were forced to alter the regimen to capecitabine and trastuzumab (X+HER). As support and home medical care by the patient's family were available, X+HER therapy was continued at an outpatient oncology unit. X+HER therapy appeared to be effective in terms of stabilizing the tumor, considering that a slight increase was noted in the stomach tumor size; moreover, the liver metastases exhibited a significant reduction, as observed on follow-up CT after the 7th course of chemotherapy (approximately 8 months after the onset of symptoms). The patient's cognitive condition was also stable (MMSE, 22/30; WMS-R: verbal memory, 77; visual memory, 61; general memory, 69; attention/concentration, 94; delayed recall, 56), and PET/CT of the brain showed a lower FDG uptake (SUVmax, 5.8) in the mesial temporal regions. Because we considered it to be a clinically stable disease, we continued X+HER therapy.

After 10 courses of chemotherapy (over a period of approximately 11 months after the onset of symptoms), the patient suffered a generalized tonic-clonic seizure and was transferred to the emergency department of our hospital. CT of the abdomen revealed multiple enlarged liver metastases and thickening of the gastric wall (Fig. 5). Despite the addition of an antiepileptic drug to his regimen, the complex partial seizures and cognitive dysfunction worsened and became uncontrollable. Given the failure of chemotherapy and the deterioration in the performance status and progressing dementia, treatment was discontinued and best supportive care was initiated. Approximately 14 months after the onset of symptoms, the patient passed away.

Discussion

Although PNSs are tumor-associated, immune-mediated syndromes, they are not caused by a local effect of the tumor or its metastases. They potentially affect any level of the nervous system and may result in motor neuron syndromes, extrapyramidal symptoms, cerebellar degeneration, myelitis, mononeuropathy, and limbic encephalitis (1). The main pathogenic effect is most likely exerted by cytotoxic T cells, resulting in neuronal cell death. The incidence of PNS is far less than 1% for solid tumors, and commonly associ-

Table. Paraneoplastic Syndromes Involving the Nervous System in Gastric Cancer.

Reference	Age (years)/Sex	Pathological Diagnosis	Neurological Syndrome	Onconeural Antibody
8	63/female	Adenocarcinoma	Subacute sensory neuropathy	Anti-Hu antibody
9	73/male	Adenocarcinoma	Subacute cerebellar degeneration	Anti-Yo antibody
10	61/male	Adenocarcinoma	Limbic and brainstem encephalitis	Anti-Ma antibody
11	63/male	Adenocarcinoma and neuroendocrine carcinoma	Subacute cerebellar degeneration	Anti-Ri antibody
12	71/male	Adenocarcinoma	Subacute cerebellar degeneration	Anti-Yo antibody
3	NA	NA	Encephalomyelitis	Anti-Hu antibody
3	NA	NA	Encephalomyelitis	Anti-Hu antibody
13	38/female	Neuroendocrine carcinoma	Neuromyelitis optica	Negative (but NMO-IgG positive)
14	72/female	Adenocarcinoma	Systemic myositis and subacute sensory neuropathy	Negative
15	59/male	Adenocarcinoma	Opsoclonus-myoclonus	Negative
16	58/male	Neuroendocrine carcinoma	Subacute cerebellar degeneration	Negative
Our case	71/male	Adenocarcinoma	Limbic encephalitis	Anti-Hu antibody

NA: information not available

ated tumor types include ovarian cancer, thymoma, and small-cell lung cancer (2). In contrast, PNSs in GC are very uncommon. A review of the literature reflecting 200 patients with anti-Hu-antibody-positive PNS showed that pathologically identified GC was present in only 1.3% of these patients (3).

Generally, paraneoplastic limbic encephalitis is classified into four groups: the anti-Hu antibody-positive group, the anti-Ma2 antibody-positive group, the anti-voltage-gated potassium channel (VGKC) antibody-positive group, and the anti-N-methyl-D-aspartate receptor (NMDAR) antibody-positive group (4). Anti-Hu and Ma antibodies target intracellular antigens, whereas anti-VGKC and NMDAR antibodies target neuronal cell-surface antigens, showing a better treatment response than that seen in diseases associated with antibodies against intracellular antigens (4). The detection of onconeural antibodies has often been useful for identifying the primary site of cancer, as several antibodies have a strong association with specific tumors and neurological symptoms (1). Anti-Ma antibodies are almost always associated with testicular germ-cell tumors. The anti-Hu antibody is highly associated with small-cell lung cancer and often results in neurological symptoms, including encephalomyelitis, encephalitis, cerebellar degeneration, and/or sensory neuropathy, that precede the diagnosis of cancer.

Moreover, Molinuevo et al. reported that the anti-Hu antibody has a high diagnostic value, with a specificity of 99% and a sensitivity of 82% (5). Aiming to identify specific onconeural antibodies and neurological symptoms in patients with GC, we performed a literature review (Table). Only 11 cases of GC patients with PNSs have been reported, and well-characterized onconeural antibodies were recognized in eight of these cases (73%). A histological confirmation of GC was obtained in nine of the 11 patients. Notably, the incidence of neuroendocrine carcinoma was striking in those patients. To the best of our knowledge, our case is the first case of anti-Hu antibody-positive limbic encephalitis in a patient with HER2-positive GC. The correlation among HER2, anti-Hu antibody, and limbic encephalitis in our case is unknown. However, in previous studies on breast cancer, HER2 overexpression was mentioned as an important requirement for developing anti-Yo-associated paraneoplastic cerebellar degeneration (6). Hence, such a correlation may be possible.

The symptoms of PNSs can be dramatic. A rapid worsening of neurological symptoms is sometimes critical in the diagnosis of PNSs. The management of PNS symptoms has been challenging, as various immunosuppressive treatments have proved to be ineffective for syndromes with onconeural antibodies. Previous studies suggest that surgical tumor removal could stabilize and even improve the clinical picture of these patients (7, 8). In the present case, the response to trastuzumab-combined chemotherapy was clinically stable disease, including stable neurological symptoms, and the SUVmax of the mesial temporal regions was 5.8 by PET/CT; however, chemotherapy eventually failed, and the patient's symptoms deteriorated, with the SUVmax of the mesial temporal regions rising to 10.8. This presentation suggests that the tumor volume corresponds to the amount of antibody and neurological symptoms. Graus et al. reported that in patients with PNS associated with the anti-Hu antibody, antineoplastic therapy was associated with recovery or stabilization, with an odds ratio of 4.56 (95% confidence interval, 1.62-12.86) (3). Thus, prompt tumor volume control

may contribute to improving symptom management, and our case suggested that molecularly-targeted, combined-drug chemotherapy could potentially be effective for the management of PNS.

In conclusion, we presented a rare case of PNS with HER2-positive GC that developed limbic encephalitis and carried anti-Hu antibodies. This case brought to our attention the fact that a prompt diagnosis and treatment are essential, as optimal chemotherapy may lead to the improvement of PNSs.

The authors state that they have no Conflict of Interest (COI).

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