Hashimoto’s Encephalopathy As the Cause of Deteriorating Consciousness During Treatment of Leptomeningeal Carcinomatosis From Breast Cancer

Case Report

A 53-year-old woman was diagnosed with breast cancer, and the pathologic results showed hormone-receptor–positive, HER2/neu–negative invasive lobular carcinoma in December 2007. The patient underwent a modified radical mastectomy followed by adjuvant chemotherapy, radiotherapy, and tamoxifen treatment immediately after the diagnosis. Unfortunately, a recurrence with a solitary brain metastasis developed in February 2009. Surgical excision of the brain tumor on February 27, 2009, confirmed the diagnosis of metastatic breast cancer. The patient received whole-brain radiotherapy (3,000 cGy per 10 fractions from March 18, 2009, to March 21, 2009) and salvage hormone therapy with letrozole for the next 2 years.

The patient suffered from progressive slurred speech and an unsteady gait in early January 2011. One episode of brief unconsciousness resulted in a fall, and the patient came to our emergency department on January 7, 2011. The brain magnetic resonance imaging (MRI) showed multiple leptomeningeal lesions without brain parenchymal metastasis. The electroencephalography (EEG) later disclosed nonconvulsive status epilepticus. Anticonvulsive drugs were used. A CSF cytology study supported the diagnosis of leptomeningeal carcinomatosis. Intrathecal chemotherapy with methotrexate 12 mg was applied on January 18, 2011. An Ommaya reservoir implantation was done, and the patient was enrolled onto a clinical trial (NCT01281696)\(^1\) of systemic chemotherapy with bevacizumab, cisplatin plus etoposide (bevacizumab 15 mg/kg intravenous (IV) infusion for 90 minutes on day 1, cisplatin 70 mg/m\(^2\) IV infusion for 3 hours on day 2, etoposide 70 mg/m\(^2\) IV infusion for 60 minutes per day from days 2 to 4, repeated every 3 weeks on January 26, 2011, and February 16, 2011, separately. The neurologic signs and symptoms of the patient improved gradually after two cycles of the chemotherapy. Follow-up CSF studies were all negative for malignant cells, and the neurologic deficit of the patient was much improved after treatment. She received the third course of systemic chemotherapy and concurrent intrathecal chemotherapy on March 8, 2011, the fourth course on March 28, 2011, and the fifth course on April 20, 2011.

However, a new neurologic deficit developed approximately 10 days after the fifth course of systemic chemotherapy and concurrent intrathecal chemotherapy. The patient suffered from subacute onset, progressive right-limb weakness and, subsequently, tremors accompanied by a depressed level of consciousness. The patient came to our emergency department on May 1, 2011. Her laboratory tests revealed a hemoglobin level of 10.6 g/dL, WBC count of 6.2 K/µL, and platelet count of 81 K/µL. The biochemistry and electrolyte parameters were all within normal limits.

A brain MRI study was performed but did not reveal any new lesions except for extensive white-matter changes. Repeated CSF cytology studies from both the Ommaya reservoir and the lumbar puncture indicated no malignant cells later. The CSF protein levels was 18 mg/dL (normal range, 70 to 110 mg/dL). No WBCs were detected in the CSF. Although the infectious process was on the list for a differential diagnosis, cultures for bacteria, virus, or fungus from all sites, including blood, CSF, sputum, and urine, were all negative. The clinical presentation of the patient, such as subacute cognitive dysfunction and possible complex partial seizure, also mimicked paraneoplastic limbic encephalitis, but the brain MRI did not demonstrate corresponding signal changes over the limbic system. Because the plasma level of valproate was within the therapeutic range, a second anticonvulsant (ie, levetiracetam) was added because of suspicion of uncontrolled complex partial seizure.

Despite intensive studies for potential etiologies, none could be determined. The EEG on May 9, 2011, showed nearly continuous diffuse sharps and slow waves from 3 to 7 Hz and 20 to 100 µV with some triphasic waves, which indicated the possibility of metabolic encephalopathy. Most of the metabolic factors, including renal function, electrolytes, hepatic function, serum adrenocorticotropic hormone, and cortisol level, were all within normal limits. Ultimately, thyroid-function tests exhibited a thyroid-stimulating hormone (TSH) level of 0.008 µU/mL (normal range, 0.1 to 4.5 µU/mL), free-T\(_4\) level of 1.26 ng/dL (normal range, 0.6 to 1.75 ng/dL), and T\(_3\) level of 190 ng/dL (normal range, 80 to 180 ng/dL). To figure out the cause of this unexplained encephalopathy, serum antithyroid antibodies were examined and were found to be markedly increased for both the antithyroglobulin (anti-TG) antibody (145.5 IU/mL), anti-TPO antibody: 1,302.5 U/ml.

**Fig 1.**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>Jan 7</td>
<td>Conscious drowsy/unsteady gait</td>
</tr>
<tr>
<td></td>
<td>MRI: Leptomeningeal carcinomatosis</td>
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<tr>
<td></td>
<td>CSF: Positive for malignant cell cytology</td>
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<td></td>
<td>EEG: Nonconvulsive status epilepticus</td>
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<tr>
<td>Jan 26</td>
<td>1st cycle of systemic chemotherapy</td>
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<tr>
<td>Apr 20</td>
<td>Conscious drowsy/right limbs weakness,</td>
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<tr>
<td></td>
<td>CSF: Negative for malignant cell from both Ommaya</td>
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<tr>
<td></td>
<td>and lumbar puncture</td>
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<tr>
<td></td>
<td>EEG: Favor metabolic encephalopathy</td>
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<tr>
<td></td>
<td>anti-TG antibody: 145.5 U/ml, anti-TPO antibody: 1,302.5 U/ml</td>
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<tr>
<td>May 1</td>
<td>Steroid pulse therapy</td>
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<tr>
<td>May 20</td>
<td>6th cycle of systemic chemotherapy</td>
</tr>
<tr>
<td>Aug</td>
<td>Conscious drowsy, CSF: Recurrence of malignant cells</td>
</tr>
</tbody>
</table>

*restart systemic chemotherapy*
Hashimoto’s thyroiditis remain controversial. Corticosteroid response than definitive evidence. The EEG and neuroimaging studies, including computed tomography, is a sensitive test but is not required for the diagnosis.3,4,5 The findings of steroid treatment. Testing for an increases of these antibodies in CSF is not associated with thyroid dysfunction, but there is still no evidence that HE may be the sequel of cancer treatments. Additional research regarding the pathogenesis of HE in malignant disease is warranted.

Some improvement has been seen in the treatment and prognosis of malignant diseases with CNS metastasis.6 It is perplexing that, when a patient with brain metastasis or leptomeningeal carcinomatosis suffers from an acute or subacute alteration of consciousness, physicians usually struggle to differentiate between malignant disease progression and other possible causes. Disease progression would have been the diagnosis if we had not conducted a meticulous review of all the clinical clues and called on the efforts of other specialists, such as neurologists and endocrinologists.

In conclusion, we report on a patient with breast cancer with leptomeningeal carcinomatosis who developed HE during her courses of chemotherapy treatment. HE, which is a rare but treatable encephalopathy, should be considered one of the differential diagnoses in conscious, disturbed patients with cancer without definite etiology after thorough investigations. Although disease progression accounts for the majority of cases in our daily practice, a discrete survey for any other possible causes needs to be kept in mind.


discussion

In this article, we presented the case of a woman with leptomeningeal carcinomatosis from breast cancer who suffered from acute neurologic deficits during systemic chemotherapy with a fair response. After ruling out the common causes of encephalopathy, such as infections, metabolic derangements, seizure, and progression of leptomeningeal carcinomatosis, we obtained a diagnosis of HE. To our knowledge, this is the first report in the literature on HE occurring with leptomeningeal carcinomatosis. This report highlights the importance of a high index of suspicion in cases with unexplained encephalopathy for early diagnosis of HE, which is a potentially treatable disease.

HE, also called steroid-responsive encephalopathy associated with autoimmune thyroiditis, is a rare or underdiagnosed disorder characterized by high titers of serum antithyroid antibodies.2 The prevalence has been estimated to be approximately 2.1:100,000 patients, with a significant preponderance of women.3 The neurologic presentation of HE is quite heterogeneous. The three most frequent manifestations include behavioral change (90% to 100%), cognitive dysfunction (80%), and seizure (60% to 70%).4 The pattern and severity of neurologic deficits are not associated with thyroid dysfunction.5,5 Most cases have developed HE at euthyroid status. The diagnosis of HE is based on clinical features, the increase of the serum anti-TPO antibody and/or the anti-TG antibody, and the response to steroid treatment. Testing for an increases of these antibodies in CSF is a sensitive test but is not required for the diagnosis.3,4,5 The findings of the EEG and neuroimaging studies, including computed tomography and MRI, are usually nonspecific and, consequently, suggestive rather than definitive evidence.

The pathogenesis of HE and the correlation between HE and Hashimoto’s thyroiditis remain controversial. Corticosteroid responsiveness supports an immune etiology, but it is uncertain whether antithyroid antibodies are associated with the direct pathogenic mechanisms or are just epiphenomenon of diverse etiologies. Through a literature search, we found only one previous article that reported the development of HE in a patient with cancer.6 Many antineoplastic agents, especially tyrosine kinase inhibitors, may lead to thyroid dysfunction, but there is still no evidence that HE may be the sequel of cancer treatments. Additional research regarding the pathogenesis of HE in malignant disease is warranted.

## Discussion

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## Authors’ Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

## References


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