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Wernicke encephalopathy in a lung cancer patient during treatment with nivolumab

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Case Report

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Abstract

Objective. Wernicke encephalopathy (WE) is a neuropsychiatric disorder caused by thiamine deficiency. It is recognized in various stages of the cancer trajectory but has not previously been recognized during nivolumab treatment.

Method. From a series of WE patients with cancer, we report a lung cancer patient who developed WE during treatment with nivolumab.

Result. A 78-year-old woman with lung cancer was referred to our psycho-oncology clinic because of depressed mood. Psychiatric examination revealed disorientation to time, date, and place, which had not been recognized 1 month previously. Her symptoms fulfilled the diagnostic criteria for delirium. No laboratory findings or drugs explaining her delirium were identified. WE was suspected as she experienced a loss of appetite lasting 4 weeks. This diagnosis was supported by abnormal serum thiamine and the disappearance of delirium after intravenous thiamine administration.

Significance of results. We found WE in an advanced lung cancer patient receiving treatment with nivolumab. Further study revealed the association between nivolumab and thiamine deficiency. Oncologists should consider thiamine deficiency when a patient experiences a loss of appetite of more than 2 weeks regardless of the presence or absence of delirium.

Introduction

Wernicke encephalopathy (WE) is a neuropsychiatric disorder caused by a deficiency of thiamine that, in its biologically active form, thiamine pyrophosphate, is necessary for oxidative metabolism (Sechi & Serra, 2007). This disorder is reversible if properly diagnosed and treated with parenteral thiamine administration; however, this disorder often goes unrecognized because of the diversity of symptoms (Isenberg-Grzeda et al., 2012; Onishi et al., 2016; Sechi et al., 2016b). If left untreated, it causes severe and irreversible brain damage (Korsakoff syndrome), leading to death. The estimated mortality rate is about 20% (Victor et al., 1971).

Recent studies have revealed that WE can be recognized in patients with cancer at several points during the cancer trajectory (Isenberg-Grzeda et al., 2016a; Onishi et al., 2004, 2016, 2017b). Nivolumab is a human immunoglobulin G4 anti-PD-1 monoclonal antibody that is used to restore antitumor immunity disturbed by cancer cells. Various side effects are recognized (Postow, 2015; Spain et al., 2017) including central nervous system side effects; however, WE has not previously been recognized during nivolumab treatment.

In this communication, we report a lung cancer patient diagnosed with WE during nivolumab treatment. Clinical suspicion, correct diagnosis, and subsequent parenteral thiamine administration relieved the symptoms, preventing irreversible brain damage and allowing resumption of the nivolumab treatment.

Case report

A 78-year-old woman with lung cancer was referred by her oncologist to the psycho-oncology outpatient clinic because of depressed mood. She had been diagnosed with lung cancer 3 years previously and had received chemotherapy. She received carboplatin and paclitaxel (Ohe et al., 2007) for about 1 year. After this, she received 43 cycles of nivolumab over an approximate 2-year period.

From 1 month before her visit to the psycho-oncology outpatient clinic, however, she could not receive nivolumab because of depressed mood, muscle weakness, ataxia, and vertigo. She could not leave home; her oncologist, therefore, referred her to our clinic.

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On her first psychiatric examination, the patient was disoriented and unable to provide the date or the name of the hospital. She was also unable to perform calculations. Neurological examination revealed ataxia, although no eye symptoms were observed. She did not develop nausea, vomiting, diarrhea, or fever. Brain magnetic resonance imaging findings revealed old cerebellar infarction and chronic ischemic lesions. Encephalitis, which is one of the neurological side effects of anti-PD-1 drugs (Spain et al., 2017), was not recognized. Further, we could not find any drug or laboratory findings to explain her delirium, including C-reactive protein, cortisol, and thyroid function. Her psychiatric features fulfilled *the Diagnostic and Statistical Manual of Mental Disorders 4th edition* criteria (American Psychiatric Association, 2000) for delirium.

The patient was a housewife who was very kind to others and had no medical history of psychiatric illness or alcohol or drug abuse. A detailed interview with her daughter revealed that her appetite had been 20% of normal for the previous 4 weeks.

We suspected WE because her loss of appetite had lasted 4 weeks and ingested thiamine is stored in the body for approximately 18 days (MacLean et al., 1983). We, therefore, administered 100 mg of thiamine intravenously, and the delirium was resolved by the following week.

Her serum thiamine level, as measured using high-performance liquid chromatography, was abnormally low at 19 ng/mL (reference range: 24–66 ng/mL), whereas her serum vitamin B12 level was within the normal range (292 pg/mL; reference range: 180–914 pg/mL). Based on these findings, she was diagnosed with WE. Three weeks after first consultation, she resumed nivolumab treatment in combination with thiamine administration.

Discussion

We experienced a lung cancer patient diagnosed with WE during treatment with nivolumab. Although her treatment was interrupted by WE, correct diagnosis and subsequent thiamine administration led to the resumption of nivolumab treatment.

Several mechanisms could have contributed to the development of WE in this patient. First, appetite loss is thought to be related. The patient had experienced a loss of appetite lasting 4 weeks. This could be associated with a thiamine deficiency because the human body is only able to store thiamine for about 18 days (MacLean et al., 1983).

Next, the effect of nivolumab might also be related. Some chemotherapeutic agents are associated with thiamine deficiency. Clinical and experimental studies have indicated that 5-fluorouracil may be associated with thiamine deficiency by increasing either the utilization or the breakdown of thiamine (Aksoy et al., 1980; Basu et al., 1979). In addition, the clinical development of fedratinib, the Janus kinase 2 inhibitor, was discontinued because it was found to inhibit thiamine uptake, leading to the development of WE (Pardanani et al., 2015; Sechi et al., 2016a; Zhang et al., 2014). Appetite loss associated with nivolumab treatment is also indirectly related to thiamine deficiency and subsequent WE. Further study is needed to clarify these relationships.

The patient did not develop all three symptoms typical of WE, including delirium, ataxia, and eye symptoms. Recent study revealed that most patients with WE symptoms do not develop all three symptoms (Isenberg-Grzeda et al., 2014, 2016b; Onishi et al., 2018); the clue to the diagnosis of this patient was appetite loss. Thiamine deficiency can occur any time nutrition is unbalanced for 2–3 weeks (Sechi et al., 2016b) because thiamine is only stored in the body for about 18 days (MacLean et al., 1983). Some patients with thiamine deficiency do not present with accompanying delirium (Isenberg-Grzeda et al., 2017; Onishi et al., 2017a, 2018); therefore, thiamine deficiency should be considered when a loss of appetite lasts more than 2 weeks, regardless of the presence or absence of delirium.

In conclusion, we found WE in an advanced lung cancer patient receiving treatment with nivolumab. Further study is expected to reveal the associations between nivolumab and thiamine deficiency. In addition, oncologists should consider thiamine deficiency if the patient experiences a loss of appetite of more than 2 weeks regardless of the presence or absence of delirium. Careful consideration of this condition will be of particular help to cancer patients.

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