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CASE REPORT

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Autoimmune Encephalitis After Treatment of Hodgkin's Lymphoma with the Immune Checkpoint Inhibitor Nivolumab

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ABSTRACT

In recent years, by the usage of new immune therapeutic agents for cancer treatment, the neurologic adverse events began to be seen more frequently. Nivolumab, one of the immune checkpoint inhibitor, is a human IgG4 antibody that blocks programmed cell death protein 1 and is approved against metastatic melanoma, squamous cell lung cancer, renal cell carcinoma, and Hodgkin's lymphoma after failure of prior line of chemotherapy. Here, we present a 40-year-old patient developing encephalopathy after treatment of Hodgkin's lymphoma with the immune checkpoint inhibitor nivolumab. In literature, cases of autoimmune encephalitis after receiving combination therapy of immune checkpoint inhibitors ipilimumab and nivolumab were described before. As far as we know, this is the unique case of encephalopathy reported after monotherapy with nivolumab treatment used for Hodgkin's lymphoma.

Keywords: Nivolumab, immune checkpoint inhibitor, autoimmune encephalitis, neuronal antigens, immune response, encephalopathy

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INTRODUCTION

Immune checkpoint inhibitors, including antibodies targeting cytotoxic T-lymphocyte-associated antigen-4 and programmed cell death protein-1, have demonstrated improved tumor related outcomes in multiple types of cancer. They act by enhancing antitumor immunity and show a unique spectrum of toxic effects. Neurologic side effects are rare and varying as immune-related adverse events of the central and peripheral nervous system including immune polyneuropathies, myasthenia gravis, posterior reversible encephalopathy syndrome, aseptic meningitis, transverse myelitis as well as immune encephalitis (1–3). In recent years, by the usage of new immune therapeutic agents for cancer treatment, the neurologic adverse events have become more common (4).

Nivolumab, one of the immune checkpoint inhibitor, is a human IgG4 antibody that blocks programmed cell death protein 1 and potentiates activation of T cells (5, 6). It is approved against metastatic melanoma, squamous cell lung cancer, renal cell carcinoma, and Hodgkin's lymphoma after failure of prior line of chemotherapy (4). Here, we present a case developing encephalopathy after treatment of Hodgkin's lymphoma with the immune checkpoint inhibitor nivolumab.

CASE REPORT

A 40-year-old man admitted to our clinic with hand tremor, stillness, confusion and imbalance since 25 days. The patient was diagnosed as Hodgkin's lymphoma in the year 2008 and went under bone marrow transplantation in 2014. He was treated with a single dose of the immune checkpoint inhibitor nivolumab one month ago. Results of his neurological examination revealed disorientation, inattention, postural tremor in the upper left extremity, and ataxia. Magnetic resonance imaging (MRI) of the brain showed right occipital, left frontal millimetric lesions with gadolinium enhancement (Figure 1). Electroencephalography revealed moderate disorganization in the frontal regions of the hemispheres and frontal intermittent rhythmic delta activity (Figure 2). Cerebrospinal fluid (CSF) analysis demonstrated mildly increased protein level (695 mg/L), normal glucose level (CSF glucose 55 mg/dL, concurrent serum glucose 112 mg/dL), normal immunoglobulin G index, positive oligoclonal bands (patern 4), pleocytosis (25 white blood cells). Results of an extensive evaluation of blood and CSF revealed no evidence of infection. The test for limbic encephalitis and paraneoplastic antibodies were all negative. Owing to the severity of the symptoms, nivolumab treatment was discontinued. Given the concern for autoimmune encephalitis, the patient was treated with intravenous corticosteroids (pulse therapy for 10 days with methylprednisolone 1000 mg daily) followed by oral methylprednisolone (32 mg daily) lasting for one month. We observed both clinical and electroencephalographic (Figure 3) significant positive responses to treatment. One month later, the patient's neurologic functioning was nearly back to baseline and in the clinical follow up no new findings occurred.

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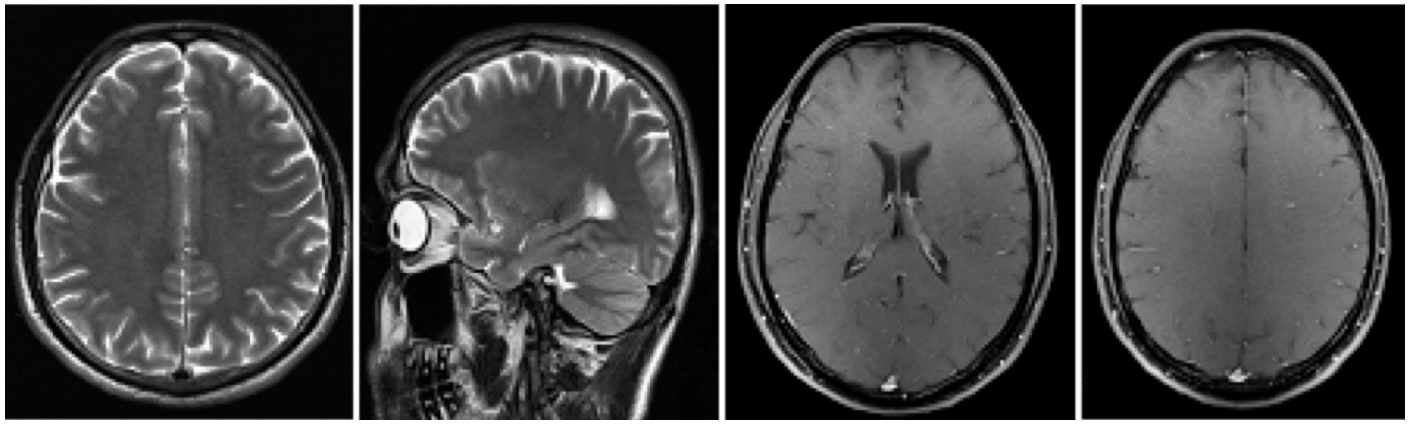

Figure 1. Brain MR revealed right occipital, left frontal, millimetric contrast enhancing foci.

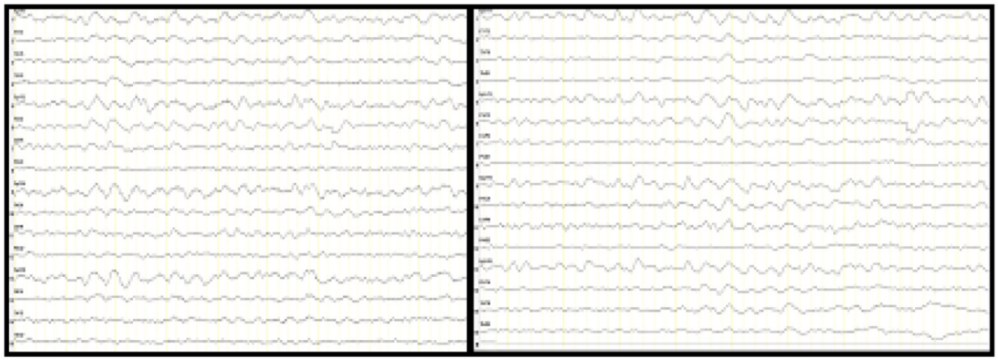

Figure 2. Electroencephalography revealed moderate disorganization in the frontal regions of the hemispheres and frontal intermittent rhythmic delta activity.

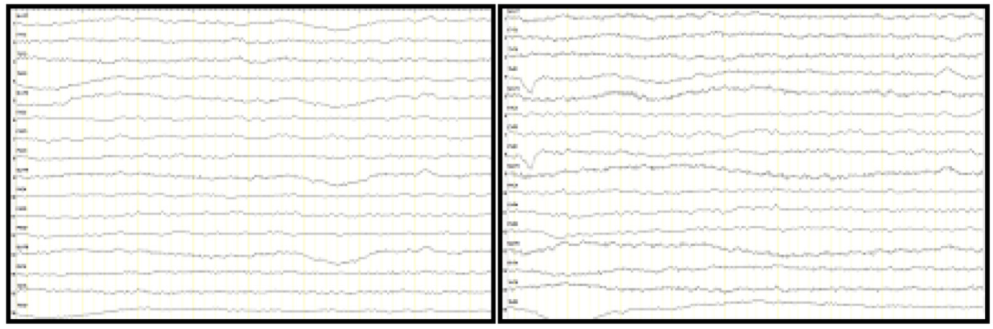

Figure 3. On ninth day of the steroid treatment, delta activity disappeared and 6.5–7 Hz teta wave activity was monitored on EEG.

DISCUSSION

Immune checkpoint inhibitors may favor the development of immune responses against neuronal antigens leading to autoimmune encephalitis. Early recognition in neurological adverse events is essential for treating patients as soon as possible for maximizing clinical recovery.

We describe a patient who developed encephalopathy after receiving therapy with immune checkpoint inhibitor nivolumab. In literature, cases of autoimmune encephalitis after receiving combination therapy of immune checkpoint inhibitors ipilimumab and nivolumab were described before. As far as we know, this is the unique case of encephalitis reported after monotherapy with nivolumab treatment used for Hodgkin's lymphoma.

Encephalitis is one of the side effect of immune check point inhibitors, and may occur at any time point. The cases described by Williams et al., and our case, all had short time intervals between the occurrence of encephalitis and drug administration. However, this strongly suggests a direct relationship between the immune checkpoint inhibitors and encephalitis; patients need further examinations to exclude all other potential causes of encephalitis. In addition, although high-dose steroid immunotherapy treatment supports the diagnosis of autoimmune encephalitis, our patient has also been screened for other causes. Complete workup showed no evidence for any other cause.

Disruption of the homeostasis of immune checkpoint inhibitors can result in uncontrolled immune response. This may lead to inflammatory or autoimmune adverse events targeting different tissues in the body (4). The relationship between the toxicities and tumor response is still unclear. So, further studies are needed to elucidate this correlation. As the number of indications for these agents increase, more patients will be exposed to them and side effects will be seen more often. So, further studies are also needed to identify patients who are more likely to develop immune adverse events to prevent these side effects. Also, early recognition and treatment of adverse events is important for obtaining complete recovery.

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