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Thiamine deficiency in a patient with recurrent renal cell carcinoma who developed weight loss with normal appetite and loss of energy soon after nivolumab treatment

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Case Report

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Abstract

Background. Nivolumab has become an effective treatment option for cancer in various sites; however, this drug may cause immune-related adverse effects due to its mechanism of action. Furthermore, little has been reported on thiamine deficiency (TD) in patients receiving nivolumab treatment.

Method. From a series of cancer patients, we reported a patient with recurrent renal cell carcinoma who developed TD after the start of nivolumab treatment.

Results. A 74-year-old man with recurrent renal cell carcinoma was referred to the psycho-oncology department as he had lost about 4 kg and displayed a loss of energy after four cycles of nivolumab treatment. Psychiatric interviews revealed a decrease in energy. Neurological examination did not reveal any impairment in consciousness, ataxia, or ocular symptoms. He did not develop appetite loss. The malabsorption or overconsumption of some nutrients is thought to occur due to the rapid loss of weight; thus, a reduction in vitamin B1, which has a short storage period in the body and is often deficient in cancer patients, was suspected. The diagnosis of TD was supported by the patient's abnormally low serum thiamine level.

Significance of results. In patients treated with nivolumab, it is necessary to pay careful attention to TD when proceeding with the treatment. It is hoped that future research may reveal the link between nivolumab administration and TD.

Introduction

Nivolumab is a human immunoglobulin G4 anti-programmed cell death 1 monoclonal antibody that is used to restore antitumor immunity disturbed by cancer cells. This drug has become an effective treatment option for cancer in various sites, and its indication is expanding. However, this drug may cause immune-related adverse effects due to its mechanism of action (Hofmann et al., 2016; Zimmer et al., 2016). Furthermore, there are a number of unconfirmed side effects.

Thiamine, in its biologically active form of thiamine pyrophosphate, is an essential coenzyme for oxidative metabolism (Sechi et al., 2016b). As this vitamin cannot be synthesized *in vivo*, the maintenance of its physiological level is dependent on external intake. However, thiamine stores in the body can be depleted in as few as approximately 18 days (MacLean et al., 1983), and serum thiamine levels decrease when a reduced dietary intake continues for two to three weeks (Sechi et al., 2016b).

Thiamine deficiency (TD) typically results in Wernicke's encephalopathy. This disorder shows a classic triad of symptoms: impaired consciousness, ataxia, and nystagmus. Treatment involves the administration of thiamine, and early detection and treatment can resolve the condition without sequelae. However, less than 20% of cases present with all three symptoms, and as the classic triad of symptoms are nonspecific, they are often overlooked due to confusion with the neuropsychiatric symptoms of other diseases (Sechi and Serra, 2007; Isenberg-Grzeda et al., 2012). Continued failure to recognize the disorder can lead to Korsakoff syndrome, resulting in severe brain complications. The mortality rate is reported to be as high as 17% (Victor et al., 1971).

Recent studies have shown that TD is present among cancer patients, with the time of onset ranging from the preoperative to terminal stage, and a variety of symptoms are also observed (Isenberg-Grzeda et al., 2015, 2016a, 2016b, 2017; Onishi et al., 2016, 2018a, 2018b, 2018c,

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2018d, 2018e, 2019). Onset is more often observed in patients who have received fluorouracil-based chemotherapy, active cancer treatment, and have weight loss within 2 months (Isenberg-Grzeda et al., 2017). However, there is only one report on TD during nivolumab treatment in cancer patients presenting with delirium (Onishi et al., 2019).

Herein, we present a case of TD in a patient with recurrent renal cell cancer who presented at our department complaining of weight loss and a loss of energy after the start of nivolumab treatment, and for whom we were able to prevent the progression of symptoms through treatment.

Case Report

A 74-year-old man was referred to the psycho-oncology department of our institution.

He had been diagnosed with renal cell carcinoma and lung metastasis 6 years prior to referral and underwent nephrectomy at that time. Postoperative chemotherapy was discontinued due to side effects. Treatment with sorafenib was initiated 4 years prior to referral due to the progression of lung metastasis; however, treatment was changed to pazopanib 3 years prior to referral due to the continued progression of lung metastasis.

Two months prior to referral, treatment with nivolumab was initiated due to liver metastasis. The administration of furosemide 10 mg was thereafter initiated due to swelling of the legs and decreased urine output. After four treatments, he was referred as an outpatient to the psycho-oncology department as he had lost about 4 kg and displayed a loss of energy.

Psychiatric interviews at the time of the examination revealed a decrease in energy. Neurological examination did not reveal any impairment in consciousness, ataxia, or ocular symptoms. The patient and his wife received a detailed interview regarding anorexia, but no loss of appetite was confirmed. In addition, no diarrhea or vomiting was observed. Furosemide 10 mg had been administered as internal medicine. Peripheral blood and biochemical findings were normal, and no specific findings were identified on head CT scans.

The malabsorption or overconsumption of some nutrients is thought to occur due to the rapid loss of weight; and thus, a reduction in vitamin B1, which has a short storage period in the body and is often deficient in cancer patients (MacLean et al., 1983; Isenberg-Grzeda et al., 2017), was suspected and blood samples showed a reduction in its serum concentration to 15 ng/mL (reference range: 24–66 ng/mL).

After three injections of 200 mg thiamine as the treatment of TD (Galvin et al., 2010), the patient's vigor recovered, and nivolumab treatment could be resumed.

Other test results revealed that his vitamin B12 concentration was within the normal range at 335 pg/mL (reference range: 180–914 pg/mL), but his zinc concentration had decreased to 53 μg/dL (reference range: 68–113 μg/dL). Nevertheless, this returned to within the normal range after two weeks of oral zinc replacement therapy.

Discussion

TD was observed in a patient with recurrent renal cell carcinoma after the initiation of nivolumab administration. Early detection and high-dose thiamine treatment improved the symptoms and treatment with nivolumab was resumed.

One case of TD in a nivolumab-treated patient, which resulted in anorexia and impaired consciousness, was previously reported (Onishi et al., 2019); however, none of the classic triad of symptoms (impaired consciousness, ataxia, and ocular symptoms) typical of Wernicke's encephalopathy were observed in the current case. A previous study has also indicated that diagnosis based on these symptoms lacks sensitivity (Isenberg-Grzeda et al., 2017).

The symptoms appearing after nivolumab administration were decreased energy and weight loss. However, the decrease in vigor has recovered after high-dose thiamine treatment. A report on improvements in the mental and physical symptoms and TD, based on a randomized controlled trial of elderly women with marginal TD using thiamine 10 mg and a placebo, revealed significant increases in appetite and general well-being (Smidt et al., 1991). In consideration of these results, the recovery of vigor in this case seems to have been related to TD.

Although there was no loss of appetite in this case, there have been a few reports of TD without any loss of appetite (Yae et al., 2005). It was a sudden weight loss that triggered the diagnosis. As a result, it was thought that some nutrient absorption or metabolic disorder had occurred, with thiamine considered to be one of the substances lost from the body within a short period of time (MacLean et al., 1983). As the symptoms of TD are variable (Sechi et al., 2016b), they should always be regarded as differential.

It is necessary to consider other causes for the TD as there was no decrease in the amount of food consumed or signs of an unbalanced diet.

A meta-analysis revealed that digestive tract disorders are a frequent side effect of immune checkpoint inhibitors (Abdel-Rahman et al., 2015). In the present case, no gastrointestinal symptoms such as diarrhea were observed; however, as the gastrointestinal tract was not reviewed, the possibility of an association could not be ruled out.

In the current case, the administration of furosemide was also begun after the start of nivolumab administration. Furosemide administration increases urinary vitamin B1 excretion (Rieck et al., 1999), and long-term, high-dose (80–240 mg) administration of diuretics in patients with heart failure, etc., may lead to a deficiency in water-soluble vitamins including vitamin B1 (Seligmann et al., 1991; Katta et al., 2016). The administration of furosemide in this case was low at 10 mg; nevertheless, it may have contributed to the TD.

In addition, the possibility that nivolumab may have increased the utilization and breakdown of furosemide, as with 5-fluorouracil (Basu et al., 1979; Aksoy et al., 1980), or resulted in a thiamine absorption disorder, as with fedranib (Pardanani et al., 2015; Sechi et al., 2016a), cannot be excluded.

The current case showed a reduction in the serum zinc level. Zinc plays an important role in cell growth, differentiation, and metabolism (Prasad, 1995), and a deficiency can, clinically, result in weight loss, a decline in immune function (Prasad, 1995; Beck et al., 1997), and other symptoms. There are no reports of zinc deficiency in cancer patients, and the symptoms of zinc deficiency are nonspecific. Nevertheless, its involvement in weight loss cannot be ruled out.

In conclusion, for patients treated with nivolumab, it is necessary to pay careful attention to TD when proceeding with treatment. It is hoped that future research may reveal the link between nivolumab administration and TD.

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