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Subclinical thiamine deficiency in patients with abdominal cancer

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Case Report

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Abstract

Objective. Thiamine is an essential coenzyme for oxidative metabolisms; however, it is not synthesized in the human body, and the average thiamine storage capacity is approximately 18 days. Therefore, thiamine deficiency (TD) can occur in any condition of unbalanced nutrition. If TD is left untreated, it causes the neuropsychiatric disorder Wernicke encephalopathy (WE). Although WE is a medical emergency, it is sometimes overlooked because most patients with WE do not exhibit all of the typical symptoms, including delirium, ataxia, and ophthalmoplegia. If all of the typical clinical symptoms of WE are absent, diagnosis of TD or WE becomes more difficult.

Method. From a series of cancer patients, we reported three patients who developed TD without the typical clinical symptoms of WE.

Result. A 69-year-old woman with pancreatic body cancer receiving chemotherapy with paclitaxel and gemcitabine for six months. Her performance status (PS) was 1. A detailed interview revealed that she had appetite loss for six months. Another 69-year-old woman with ovarian cancer received nedaplatin; her PS was 0. A detailed interview revealed that she had appetite loss for three months. A 67-year-old woman with colon cancer receiving ramucirumab in combination with second-line fluorouracil with folinic acid and irinotecan. Her PS was 1. A detailed interview revealed that she had appetite loss for three weeks. None exhibited typical clinical signs of WE, but they developed appetite loss for six months, three months, and three weeks, respectively. The diagnosis of TD was supported by abnormally low serum thiamine levels.

Significance of the results. This report emphasizes the possibility of TD in cancer patients even when patients do not develop typical clinical signs of WE. The presence of appetite loss for more than two weeks may aid in diagnosing TD. Patients receiving chemotherapy may be at greater risk for developing TD.

Introduction

Thiamine, in its biologically active form, thiamine pyrophosphate, is an essential coenzyme for oxidative metabolisms (Sechi et al., 2016b). However, it is not synthesized in the human body, and the average storage capacity of thiamine is approximately 18 days (MacLean et al., 1983), which is far shorter than that of vitamin B12 (5–10 years) (Shipton & Thachil, 2015). Therefore, thiamine deficiency (TD) can occur in any condition of unbalanced nutrition that lasts two to three weeks (Sechi et al., 2016b). Wernicke encephalopathy (WE) is a neuropsychiatric disorder caused by severe acute/subacute TD. This disorder is a medical emergency because it may cause severe and irreversible brain damage if left untreated (Korsakoff syndrome), leading to death in approximately 20% of patients (Victor et al., 1971).

The classical triad of symptoms of WE are mental status changes, gait ataxia, and ophthalmoplegia; however, this triad, although nearly specific to WE, has been documented in only 16% of patients in postmortem studies, and approximately 11% of patients in clinical studies (Harper et al., 1986; Isenberg-Grzeda et al., 2016). Nineteen percent of autopsy samples indicated none of the three clinical symptoms (Harper et al., 1986); therefore, the best aid for diagnosing WE, particularly in patients with cancer, is clinical suspicion (Sechi & Serra, 2007).

In our last report (Onishi et al., 2017), we described WE patients without delirium. They developed ataxia only of the three classical signs of WE. Appetite loss for longer than two weeks was the clue leading to the diagnosis (Onishi et al., 2017; Sechi et al., 2016b).

However, little is known about the subclinical manifestations of TD in patients with cancer.

In this communication, we report three TD patients with abdominal cancer without the classical triad of WE, other uncommon symptoms or signs at presentation, including stupor,

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hypotension and tachycardia, hypothermia, bilateral visual loss and papilledema, epileptic seizures, hearing loss, hallucinations, and behavioral disturbance (Sechi et al., 2016a). Clinical suspicion, correct diagnosis, and treatment with parenteral thiamine administration prevented disease progression.

Case reports

Case 1

A 69-year-old woman with pancreatic body cancer was referred by her oncologist to the psycho-oncology outpatient clinic because of anxiety and insomnia. She was diagnosed with pancreatic body cancer three months before and received surgery followed by chemotherapy. She was a home care worker who worked continuously; however, she resigned after the diagnosis of cancer. She was very kind to others and had no medical history of psychiatric illness or alcohol or drug abuse.

On her first psychiatric examination, she said that her daily activities had significantly changed after resigning. She also said that resigning caused her to lose her purpose in life. Her husband said that she was anxious about her future since the cancer diagnosis.

Her psychiatric features fulfilled the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) (American Psychiatric Association, 2013) criteria for adjustment disorder with anxiety.

She received individual and group psychotherapy, and her anxiety improved.

Fourteen months after the first consultation at the psycho-oncology outpatient clinic, a detailed interview revealed that her appetite was 60% of normal for six months. At this time, however, she was very active and her Eastern Cooperative Oncology Group performance status (PS) was 1 (Oken et al., 1982). She received chemotherapy with paclitaxel and gemcitabine for six months, and the most recent chemotherapy session was performed two weeks prior. Nausea, vomiting, and diarrhea were not noted. The neurological examination was unremarkable. In particular, the classical triad of WE was absent, as were the other uncommon symptoms or signs indicative of WE (Sechi et al., 2016a).

Although she was active in her daily life and exhibited no clinical signs of WE, we suspected TD because she developed appetite loss for six months. Because the storage capacity of thiamine is approximately 18 days (MacLean et al., 1983), we examined her serum thiamine level and then administered 100 mg of thiamine intravenously.

Her serum thiamine level measured using high-performance liquid chromatography was 15 ng/mL (reference range: 24–66 ng/mL). Thus, she was diagnosed with subclinical TD and treated accordingly.

Case 2

A 69-year-old woman with ovarian cancer was referred by her oncologist to the psycho-oncology outpatient clinic because of anxiety and depression. She was diagnosed with ovarian cancer three years before and had received chemotherapy since then, but her disease progressed.

On her first psychiatric examination, she exhibited depression and was anxious about the progression of her disease despite chemotherapy. She was unable to accept the current situation. She was active in her daily life and her PS was 0. She was given nedaplatin six weeks prior. Vomiting and diarrhea were not noted.

She was a kindergarten teacher who was very kind to others and had no medical history of psychiatric illness or alcohol or drug abuse. Her psychiatric features fulfilled the DSM-V (American Psychiatric Association, 2013) criteria for adjustment disorder with mixed anxiety and depression.

A detailed interview revealed that her appetite was 30% of normal for three months.

The neurological examination was unremarkable. In particular, no overt signs or symptoms indicative of WE were found. Although she exhibited no clinical signs of WE, we suspected TD because of the short time ingested thiamine is stored in the body (MacLean et al., 1983) and her appetite loss had lasted for three months. We examined her serum thiamine level and then administered 100 mg of thiamine intravenously.

Her serum thiamine level measured using high-performance liquid chromatography was 18 ng/mL (reference range: 24–66 ng/mL). Thus, she was diagnosed with subclinical TD and treated accordingly.

Case 3

A 67-year-old woman with colon cancer was referred by her oncologist to the psycho-oncology outpatient clinic because of anxiety and fear of chemotherapy. She had been diagnosed with colon cancer three months before, and received surgery followed by chemotherapy with capecitabine plus oxaliplatin (Cassidy et al., 2008) and bevacizumab. During the first cycle of chemotherapy, she experienced diarrhea and limb numbness. After this, she became unsure about continuing chemotherapy because she feared the side effects.

On her first psychiatric examination, she was anxious about her disease and the side effects of chemotherapy. She was unable to decide whether to continue or stop the chemotherapy. She was able to do housework and her PS was 1.

She was a housewife who was very kind to others and had no medical history of psychiatric illness or alcohol or drug abuse. Her psychiatric features fulfilled the DSM-V (American Psychiatric Association, 2013) criteria for adjustment disorder with anxiety. She received psychotherapy and her anxiety disappeared. She decided to continue chemotherapy.

Four months after the first consultation at the psycho-oncology outpatient clinic, a detailed interview revealed that her appetite was 20% of normal for three weeks after the new chemotherapy regimen (ramucirumab in combination with second-line fluorouracil with folinic acid and irinotecan) (Tabernero et al., 2015) was started.

She said that she lost 2.5 kg in one week, corresponding to 7.5% of her total body weight. Her PS was 1. The neurological examination was unremarkable. Delirium, ophthalmoplegia, and ataxia were not noted.

Although she exhibited no clinical signs of WE, we suspected TD (MacLean et al., 1983) and her appetite loss lasted three weeks. We examined her serum thiamine level and then administered 100 mg of thiamine intravenously.

Her serum thiamine level measured using high-performance liquid chromatography was 18 ng/mL (reference range: 24–66 ng/mL). Thus, she was diagnosed with subclinical TD and treated accordingly.

Discussion

We examined three patients with different abdominal cancers and diagnosed them with TD without overt clinical signs or symptoms

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indicative of WE. These patients demonstrate the diversity of clinical symptoms in TD, as our and other groups have repeatedly emphasized (Isenberg-Grzeda et al., 2016; Onishi et al., 2016, 2017; Onishi et al., 2016; Sechi et al., 2016b).

Diagnosis of TD in these patients was difficult because they were active in their daily life and did not develop the classical clinical triad or present with other uncommon signs/symptoms indicative of WE.

The clue to the diagnosis in these patients was the recognition of a recent, significant loss of appetite. TD can occur in any condition of unbalanced nutrition that lasts for two to three weeks (Sechi et al., 2016b) because of thiamine's short storage duration (MacLean et al., 1983). In our previous paper, appetite loss for two weeks led to the suspicion of WE (Onishi et al., 2017). Appetite loss for two weeks or longer may indicate thiamine deficiency, but further studies are needed to confirm this.

Another clue to the diagnosis was the use of chemotherapy. Patient 3 received 5-fluorouracil and capecitabine, which is a prodrug of 5-fluorouracil. Use of 5-fluorouracil may be associated with thiamine deficiency by increasing either the utilization or breakdown of thiamine (Aksoy et al., 1980; Basu et al., 1979;).

Cancer patients receiving fluorouracil-based chemotherapy who were referred for psychiatric consultation were significantly more likely to have TD (Isenberg-Grzeda et al., 2017). All three patients received chemotherapy. Appetite loss from the side effects of chemotherapy may be indirectly associated with thiamine deficiency.

Although the serum thiamine levels in these three patients were abnormally low, they did not develop any of the classical symptoms of WE. This neuropsychiatric syndrome usually develops when approximately 80% of body thiamine stores are depleted, if particular genetic variations in thiamine transporters occur, or when there is biochemical interference from specific types of chemotherapy with cellular thiamine transport and activation, which may occur in patients with cancer (Guerrini et al., 2009; Sechi et al., 2016a). Furthermore, circulating levels of thiamine and its isoforms may not reflect the thiamine concentration in the central nervous system (Isenberg-Grzeda et al., 2015; Thomson et al., 2010).

In conclusion, oncologists must always consider the possibility of subclinical thiamine deficiency even if the patients exhibit no classical signs of WE because thiamine deficiency can occur in any condition of unbalanced nutrition that lasts for two to three weeks (Sechi et al., 2016b). In outpatient settings, oncologists should question patients about appetite loss. Appetite loss for more than two weeks may be helpful for diagnosing subclinical TD, and patients receiving chemotherapy may be at greater risk for developing TD and WE.

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