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Can depressed cancer patients with a borderline thiamine concentration develop deficiency within a short time period?

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Case Report

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Abstract

Background. Despite increasing reports of thiamine deficiency (TD) among cancer patients, there remain some patients with borderline thiamine concentrations (BTC). However, it is unclear whether such patients subsequently develop TD.

Methods. Here, we report cases of cancer patients progressing to TD within a short time period after presentation with BTC (24–28 ng/ml).

Results

Case 1. A 49-year-old female with lung cancer. During treatment for depression, the patient showed a decreased appetite, and a blood sample revealed BTC (25 ng/ml). Fourteen days later, she reported a continued loss of appetite, and despite the absence of the 3 classical signs of Wernicke encephalopathy (WE), additional testing showed a thiamine level of 23 ng/ml, leading to a diagnosis of TD.

Case 2. A 65-year-old female developed depression during chemotherapy for angiosarcoma. Her blood sample revealed BTC (25 ng/ml). Seven days later, despite the absence of the classical signs of WE, a further testing revealed a thiamine level of 20 ng/ml.

Case 3. A 41-year-old female developed depression during chemotherapy for ovarian cancer. No loss of appetite was observed, but a blood sample revealed BTC (25 ng/ml). Seven days later, despite the absence of the classical signs of WE or decreased appetite, further testing revealed a thiamine level of 19 ng/ml.

Significance of results. Depressed cancer patients with BTC may develop TD within a short time frame. To prevent TD, health-care professionals should maintain an awareness of its potential and the need for regular testing of thiamine level or prophylactic replacement therapy.

Introduction

Thiamine, in its biologically active form thiamine pyrophosphate, is an essential coenzyme for oxidative cellular metabolism (Sechi et al. 2016).

As thiamine cannot be produced within the body, it must be taken in from an outside source. However, the body's store of thiamine can be depleted within as few as 18 days, and thiamine deficiency (TD) can occur when a loss of appetite continues for 2–3 weeks (Sechi et al. 2016). Deficiency can lead to damage to the central nervous system, which depends on glucose as an energy source. Wernicke encephalopathy (WE) is a neuropsychiatric disorder that is caused by TD (Sechi and Serra 2007). Typical symptoms are impaired consciousness, nystagmus, and ataxia, but 16% of cases present without this classical triad of signs, and about 19% of cases are asymptomatic (Harper et al. 1986). Treatment of this disease involves intravenous thiamine administration, and the condition can be resolved without sequelae by early detection and treatment. Nevertheless, WE is often overlooked due to its nonspecific symptoms and the existence of asymptomatic cases. If such a situation continues, Korsakoff syndrome can develop, leading to irreversible brain damage, so early detection and treatment are essential.

There are increasing reports of TD and WE among cancer patients (Isenberg-Grzeda et al. 2012, 2017; Ito et al. 2021; Onishi et al. 2021). Even among these reports, it can be seen that few cases present with the classical triad of signs of WE. There are also reports

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of cancer patients with thiamine levels near the lower limit of the normal range (a borderline level), and these patients also fail to show all 3 of the classical signs of WE (Barbato and Rodriguez 1994).

At present, the most useful method of diagnosing TD is clinical suspicion (Sechi and Serra 2007). Therefore, there is a need for a detailed clinical analysis of TD. However, to the best of our knowledge, there are no reports to date on patients with a normal but low (i.e., borderline) thiamine levels that progresses to TD.

Here, based on our follow-up of depressed cancer patients with low thiamine levels, we report patients who developed TD within a short period of time.

As it is reported that the normal thiamine level is 28 ng/ml or more, based on the analysis of 602 cases by the High Performance Liquid Chromatography method method (Ihara et al. 2010), a borderline value in this report was defined as less than 28 ng/ml.

Case reports

Case 1

A 49-year-old female with no history of alcohol dependence or diabetes.

The patient was diagnosed with lung cancer and brain metastases, and anticancer drug treatment was started. Two months later, signs of depression appeared and she was referred to the Department of Psycho-oncology. Depressive mood, decreased motivation, sleep disorders, decreased appetite, inhibition, difficulty concentrating, feelings of self-condemnation, and suicidal ideation were noted. Her psychiatric features fulfilled the criteria set out in The Diagnostic and Statistical Manual of Mental Disorders 5th edition for major depressive disorder (American Psychiatric Association 2013), and drug therapy with antidepressants was started.

Fourteen months after her first visit to the Department of Psychiatry and Oncology, her depression was not in remission and she was receiving pembrolizumab for cancer as well as levetiracetam 1000 mg, rebamipide 300 mg, rabeprazole 10 mg, aripiprazole 12 mg, amitriptyline 25 mg, clonazepam 4 mg, and gabapentin enacarbil 300 mg. Her appetite had reportedly decreased by about 70% in comparison to that when she was in good health, and a blood sample was taken in consideration of the possibility of vitamin B1 deficiency. Her thiamine concentration was found to be 25 ng/ml (reference range: 24–66 ng/ml), which is borderline. When she was again examined 2 weeks later, her appetite loss remained at the same level. Although none of the 3 signs of WE were observed, based on her continuing loss of appetite and the previous borderline thiamine level, a further blood sample was taken. Her thiamine level was revealed to be 23 ng/ml, and she was diagnosed with TD.

She received VB1 100 mg intravenously, but no change in the symptoms of major depressive disorder was observed after administration.

Case 2

A 65-year-old female with no history of alcohol dependence or diabetes.

The patient was diagnosed with hemangiosarcoma 21 months before her visit to the Department of Psycho-oncology because of anxiety, and she was undergoing anticancer drug treatment with paclitaxel. Depressive mood, decreased motivation, sleep disorders, inhibition, malaise, and difficulty in concentrating were noted. She was receiving mirogabalin 20 mg, vonoprazan 10 mg, olmesartan 20 mg, naldemedine 0.2 mg, alprazolam 1.2 mg, and oxycodone 30 mg. Her psychiatric features fulfilled the criteria set out in The Diagnostic and Statistical Manual of Mental Disorders 5th edition for major depressive disorder (American Psychiatric Association 2013), and drug therapy was started. Her appetite decreased to about 50%, and it continued at that level for more than 2 weeks. On taking a blood sample, her thiamine level was found to be borderline at 25 ng/ml (reference range: 24–66 ng/ml). At an outpatient visit 7 days later, her insomnia was found to have improved. She did not present with any of the 3 signs of WE, but her appetite loss continued, and a further blood test due to her previous borderline thiamine level revealed her level to be 20 ng/ml, and a diagnosis of TD was made.

She received VB1 200 mg intravenously, but no change in the symptoms of major depressive disorder was observed after administration.

Case 3

A 41-year-old female with no history of alcohol dependence or diabetes.

She was diagnosed with ovarian cancer and peritoneal metastasis 2 weeks before and underwent ovarian tumor resection 1 week before referral to the Department of Psychiatric Oncology for postoperative anxiety.

The diagnosis at her initial visit was adjustment disorder, but 1 week later, depressive mood, inhibition, malaise, difficulty concentrating, and feelings of self-condemnation became prominent. She was receiving rivaroxaban 15 mg, magnesium oxide 990 mg, loxoprofen 180 mg, rebamipide 300 mg, eszopiclone 2 mg, and metoclopramide 15 mg. Her psychiatric features fulfilled the criteria set out in The Diagnostic and Statistical Manual of Mental Disorders 5th edition for major depressive disorder (American Psychiatric Association 2013). Mirtazapine 7.5 mg was started as the drug therapy. No decrease in appetite was observed, but blood samples taken as chemotherapy (dose-dense TC) was also ongoing, which showed a borderline thiamine level of 25 ng/ml.

At the outpatient clinic 15 days later, no remission of depression was observed. Although none of the classical triad of signs of WE or a decrease in appetite was observed, a blood sample was again taken, due to the ongoing chemotherapy, and TD was diagnosed based on the observed level of 19 ng/ml.

The patient received VB1 100 mg intravenously, but no change in symptoms of major depressive disorder was observed between before and after administration.

Discussion

We experienced cancer patients who progressed from borderline thiamine levels to TD within a short period of 7 to 15 days. The results of our study are congruent with the pharmacokinetic parameters that, in humans, tissue storage of thiamine is very limited. In particular that the depletion of body stores of this vitamin can occur rapidly, after 2–3 weeks of unbalanced nutrition in healthy individuals and after 3–5 days in patients with chronic diseases (Sechi et al. 2021).

TD can lead to serious brain damage if detected late, and as the symptoms are nonspecific and there are many asymptomatic cases, it is often overlooked; thus, special attention should be paid to patients with possible TD, and the results of the cases presented

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Table 1. Treatment and clinical symptoms at initial and second blood sampling

	Case 1	Case 2	Case 3
Age	49	64	41
Sex	F	F	F
Primary site	Lung	Angiosarcoma	Ovary
Distant metastasis	Brain	N	Peritoneum
Diabetes	N	N	N
Condition at initial blood sampling			
Cancer treatment received within previous 2 weeks			
Surgery	N	N	Y
Radiation therapy	N	N	N
Chemotherapy	Y	Y	Y
Opioids	N	N	N
Psychological status			
Depression	Y	Y	Y
Remission	N	N	N
Thiamine related			
Impaired consciousness	N	N	N
Ataxia	N	N	N
Nystagmus	N	N	N
Loss of appetite	Y	Y	N
Total thiamine concentration (ng/mL)	25	25	25
Condition at second blood sampling			
Days elapsed	14	7	15
Cancer treatment received within previous 2 weeks			
Surgery	N	N	N
Radiation therapy	N	N	N
Chemotherapy	Y	Y	Y
Opioids	N	Y	N
Psychological status			
Depression	Y	Y	Y
Remission	N	N	N
Thiamine related			
Impaired consciousness	N	N	N
Ataxia	N	N	N
Nystagmus	N	N	N
Loss of appetite	Y (70)	Y (50)	N
Total thiamine concentration (ng/mL)	23	20	19

Abbreviations: Y: present, N: absent.

herein show that caution is required as cancer patients with borderline thiamine levels may progress to TD within a short period of time (Table 1).

In the cases presented herein, chemotherapy is cited as one reason for the progression to TD within a short period of time from the first examination. A previous study has reported that the rate of decreased thiamine level is high in patients receiving anticancer drugs (Isenberg-Grzeda et al. 2017). It is also known that anticancer drugs increase the utilization of thiamine and lead to its depletion in the body (Aksoy et al. 1980; Basu et al. 1979). There are also reports of deficiency in patients taking immune checkpoint inhibitors (Onishi et al. 2019, 2020a).

The second reason for the progression to TD was decreased appetite. The store of thiamine accumulated in the body is depleted within 2 or 3 weeks, and when a loss of appetite continues for several weeks, TD is likely to develop. This was also observed in the cases presented herein; appetite decreased by about 70% and 50%, respectively, in Case 1 and Case 2. However, the was no loss of appetite in Case 3. It should be noted that dietary intake alone cannot prevent the development of TD as there are reports of TD in patients with normal dietary intake (Onishi et al. 2020b).

It is not uncommon for outpatients to visit the hospital about once a month. Given the progression of TD in the meantime, prophylactic thiamine administration may be required.

Depression is the third reason for the progression to TD. All 3 cases presented herein were suffering from depression. Diagnostic criteria for depression in patients include continued loss of appetite for more than 2 weeks (American Psychiatric Association 2013). A loss of appetite is also common during treatment for depression. This also overlaps with the period of TD onset (Sechi et al. 2016). There are also reports of TD in depressed patients (Oudman 2020). Thus, cancer patients with depression may be more likely to present with TD. However, given that decreased appetite can lead to TD regardless of depression (Sechi et al. 2016), factors other than depression may also be involved.

This case report has some limitations. First, this report only presents 3 cases and does not examine all patients with low thiamine values. Second, as the subjects were psychiatric patients, the effects of mental illness cannot be ignored. Third, the current study measured thiamine levels in whole blood. Measurement of thiamine concentration in whole blood provides the sum of free thiamine present in serum or plasma, and mono- and diphosphorylated thiamine present in erythrocytes and leukocytes, and this value is said to reflect the amount of thiamine in tissues (McCormick and Greene 1994) On the other hand, measurement of serum thiamine concentration differs in that it measures only free thiamine, although it is also used to measure TD in clinical settings (Isenberg-Grzeda et al. 2017).

In conclusion, we experienced 3 cancer patients who progressed to TD within a short period of 7 to 15 days after showing a borderline thiamine value on blood tests. If a borderline thiamine level is observed, regardless of the presence of appetite loss or anticancer therapy, it may be necessary to carry out continuous testing for thiamine concentration testing or prophylactic thiamine administration, based on the fact that thiamine level may decrease within about 7 to 15 days.

In the future, we plan to verify this report by conducting studies based on a larger number of cases.

Conflicts of interest. None declared.

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