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# Subclinical thiamine deficiency: What is the most appropriate method of diagnosis and treatment?

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**Case Report**

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## Abstract

**Objectives.** The symptoms of thiamine deficiency vary considerably and asymptomatic cases; i.e., subclinical thiamine deficiency (SCTD), are known to exist. However, there is no information available on the treatment of SCTD.

**Methods.** We report a patient who underwent intravenous thiamine replacement therapy for about a month after being diagnosed with SCTD, but who developed SCTD again about three weeks after finishing the treatment.

**Results.** The patient was a 64-year-old woman who, after starting treatment for cervical cancer, complained of anxiety and underwent an initial psychiatric examination. The psychiatric diagnosis was an adjustment disorder. Based on the possibility of SCTD complications due to her decreased appetite and weight loss, her serum thiamine concentration was measured and found to be low. Therefore, thiamine was administered intravenously for 29 days. At the end of treatment, thiamine administration was discontinued as there were no apparent neuropsychiatric symptoms or problems with appetite. Twenty-three days later, there were still no problems with appetite or neuropsychiatric symptoms, but a follow-up blood sample revealed that her serum thiamine was again below the normal range.

**Significance of results.** Currently, there is no information available regarding the diagnosis and treatment of SCTD in cancer patients. In some cases, such as this case, the deficiency recurs without any symptoms indicative of SCTD; therefore, further examination for diagnosis and treatment is necessary.

## Introduction

Thiamine, in its biologically active form thiamine pyrophosphate, is an essential coenzyme for oxidative cellular metabolism (Sechi et al., 2016b). However, as thiamine cannot be produced in the body, humans are dependent on external intake. The physiological stores can be depleted within 18 days (MacLean et al., 1983) so that thiamine deficiency may occur after a loss of appetite that continues for two to three weeks. When thiamine deficiency occurs, the central nervous system, which is dependent on glucose as an energy source and consumes a large amount of energy, can easily be damaged. Wernicke encephalopathy (WE) is a neuropsychiatric disorder known to be caused by thiamine deficiency (Sechi and Serra, 2007). The treatment of this disease is the intravenous administration of thiamine, and early detection and treatment allow the disease to be resolved without sequelae. However, this disease presents with a wide variety of symptoms and, as many cases are asymptomatic, it is often overlooked (Sechi et al., 2016a; Onishi et al., 2017). If left untreated, Korsakoff syndrome may develop, resulting in irreversible brain damage and a high mortality rate of 20%. At present, the most useful diagnostic tool for WE is clinical suspicion (Sechi and Serra, 2007).

The Royal College of Physicians (RCP) and the European Federation of Neurological Societies have published guidelines for WE treatment (Thomson et al., 2002; Galvin et al., 2010). In each case, the diagnostic range is wide, and high-concentration thiamine administration is recommended. However, the results of a Cochrane review regarding the treatment of WE show that the dose, frequency, and duration of thiamine treatment are insufficient to effectively guide clinicians (Day et al., 2013). Furthermore, there is little information available regarding thiamine deficiency in cancer patients.

We identified subclinical thiamine deficiency (SCTD) in a patient undergoing treatment for cervical cancer and continued thiamine treatment for about 1 month. Thereafter, the patient



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showed no apparent neuropsychiatric symptoms nor loss of appetite and she was not in a state of clinical thiamine deficiency but, on reexamination 23 days later, SCTD was again observed. Based on this case, we would like to consider the diagnosis and treatment of SCTD and the blood sampling criteria for thiamine.

## Case report

A gynecological oncologist referred a 64-year-old cervical cancer patient to the Psycho-oncology Department (at our institution).

The patient was diagnosed with Stage IIb cervical cancer (histological type was squamous cell carcinoma) 30 days prior to her consultation. Concurrent chemoradiotherapy (CCRT) was started as a standard treatment (Green et al., 2005; Rose et al., 2007; Toita et al., 2012). Her Planned CCRT schedule was as below; radiation therapy consists of external beam radiation therapy (EBRT) with whole pelvic radiotherapy 30 Gy/15 fs and midline block 20 Gy/10 fs, and intracavitary brachytherapy (ICBT) with 24 Gy/6 fs. Chemotherapy consists of weekly cisplatin at a dose of 40 mg/m$^2$ which was administered for six courses during EBRT. She received two cycles of chemotherapy 13 and 7 days and EBRT with 22 Gy/11 fs before the scheduled consultation. However, after the second cycle of chemotherapy, she experienced dehydration due to nausea and frequent vomiting and, as a result, she underwent emergency hospitalization after being examined by a gynecological oncologist two days before the consultation. She became more anxious after admission and visited the Psycho-oncology Department for a consultation at her own request.

During her consultation, the patient complained that she was worried about her future treatment as well as her own future after being diagnosed with cancer. A loss of appetite had caused her to lose 8 kg in 2 months. No decrease in motivation, psychomotor depression, sense of self-responsibility, or suicidal ideation were noted.

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

Neurologically, no consciousness disorders, ataxia, or ocular symptoms were observed. Based on the loss of appetite, weight loss of 8 kg in 2 months, the depletion of thiamine stores in the body within about 18 days (MacLean et al., 1983), and the potential for thiamine deficiency even in patients without WE (Harper et al., 1986; Onishi et al., 2017), we provided a prophylactic administration of thiamine (100 mg) and vitamin B12 (1 mg) in consideration of the possibility of thiamine deficiency complication. Several days later, the patient's serum thiamine concentration was found to be 12 ng/mL (reference range: 24–66 ng/mL) and that of VB12 was 161 pg/mL (reference range: 180–914 pg/mL), which were abnormally low. She was discharged from the hospital after the intravenous administration of 200 mg thiamine and 2 mg vitamin B12 for 29 consecutive days.

During this time, she received three courses of chemotherapy and remaining radiotherapy.

During her stay in the hospital, her mental condition improved and her appetite improved. No particular change in neurological symptoms was observed before or after the end of the vitamin B1 treatment. Since she had no problem with her appetite, we decided to monitor her course without vitamin B1 administration at the time of discharge.

Twenty-three days after discharge, the patient has revisited Psycho-oncology Department. No physical or neurological symptoms were observed on the medical examination, and both the patient and her family reported that she had been mentally stable since discharge and had a normal appetite. She was deficient in vitamin B1 and B12 at the time of admission, so her vitamin B1 and B12 concentrations were again measured for evaluation. Her serum VB1 concentration was found to be 21 ng/mL, which was again below the reference range. Her VB12 concentration was 1,090 pg/mL, which was above the upper limit of the reference range. VB1 replacement therapy was provided, but no change in clinical symptoms was observed before or after administration. Currently, the patient is receiving 75 mg/day of VB1 orally. At 3 months after the resumption of replacement therapy, her VB1 concentration was 90 ng/mL and VB12 concentration was 915 pg/mL, which exceed the upper limits of the reference ranges. Further, no notable neuropsychiatric findings were observed.

## Discussion

We treated a patient with SCTD with 200 mg/day of thiamine intravenously for 29 consecutive days. At the end of treatment, her appetite was normal and no neuropsychiatric symptoms were observed, so thiamine administration was discontinued. Twenty-three days later, despite none of the three classical signs of WE or any clinical symptoms indicative of thiamine deficiency, her serum thiamine concentration was measured as part of her follow-up and was found to be below the reference value again. During this time, the patient's appetite did not decrease, and she did not receive any anticancer drugs or radiation treatment.

Two clinical questions arise from this case.

The first is setting the thiamine administration period for cancer patients with SCTD. Currently available evidences suggest (1) high-dose parenteral thiamine should be initiated immediately to ensure adequate and rapid penetration of this vitamin into the brain, in all patients in whom Wernicke's encephalopathy is suspected. (2) In individuals with SCTD, without defects of thiamine intestinal absorption, this vitamin should be given by mouth three times daily, considering the short half-life of thiamine (Sechi, 2020). The supplementation should be continued for several months, until deemed necessary, at a dose of at least 30 mg thrice daily (Sechi and Serra, 2007). This case suggests that thiamine deficiency may occur again after thiamine replacement therapy. Therefore, the length of thiamine replacement treatment remains a topic for further study.

There is another clinical question. In this case, thiamine deficiency after replacement therapy was accidentally found in a blood sample taken for follow-up and was not suspected based on clinical symptoms. We have previously reported cancer patients with SCTD, with the main symptom being decreased appetite (Onishi et al., 2017; Onishi et al., 2019). Even when there is no loss of appetite, there are also cases in which loss of motivation triggered the diagnosis (Onishi et al., 2020). In this case, no decrease in appetite was observed after discharge. In addition, there were no clinical symptoms indicative of thiamine deficiency. To date, only one study has examined the association between thiamine deficiency and treatment in cancer patients, with thiamine deficiency being more likely in patients within 2 months of treatment (Isenberg-Grzeda et al., 2017). This case corresponds to this condition; however, such cases are often found in cancer treatment. Taken together with this study, such results

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suggest that many cancer patients may require regular blood sampling for thiamine measurement. Further research is needed regarding the blood sampling criteria for SCTD patients who do not exhibit any neuropsychiatric symptoms.

In conclusion, we accidentally identified SCTD in a patient 23 days after the intravenous administration of 200 mg of vitamin B1 for about 1 month; however, we believe that there is a possibility that many similar patients exist. In the future, it is necessary to examine the treatment of SCTD, such as the method of diagnosis, the thiamine dose, and the duration, in cancer patients.

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