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Nonalcoholic Thiamine-Related Encephalopathy (Wernicke-Korsakoff Syndrome) Among Inpatients With Cancer: A Series of 18 Cases

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Abstract

Background—Wernicke-Korsakoff Syndrome (WKS) is a neuropsychiatric syndrome caused by thiamine deficiency. Cancer predisposes to thiamine deficiency through various mechanisms. Although many case reports exist on nonalcoholic WKS in cancer, larger qualitative studies are lacking.

Method—Retrospective study of patients admitted to a cancer hospital and diagnosed with WKS during routine care on a psychiatric consultation service. Only patients with at least 1 additional supporting feature (magnetic resonance imaging findings, low serum thiamine concentrations, or response to treatment) were included. Data pertaining to demographics, risk factors, phenomenology, and outcomes were abstracted from medical records by chart review.

Results—In all, 18 patients were included. All patients developed WKS during cancer treatment. Hematologic malignancy, gastrointestinal tract tumors, low oral intake, and weight loss were common risk factors. All patients presented with cognitive dysfunction, most commonly impaired alertness, attention, and short-term memory. All were diagnosed by operational criteria proposed by Caine et al., 1997 (where 2 of the following are required: nutritional deficiency, ocular signs, cerebellar signs, and either altered mental status or mild memory impairment). Few exhibited Wernicke's classic triad. Diagnostic and treatment delay were common. Only 3 patients recovered fully.

Conclusion—Nonalcoholic WKS can occur during cancer treatment and manifests clinically as delirium. Diagnosis should be made using operational criteria, not Wernicke's triad. Most patients were not underweight and had normal serum concentration of vitamin B_{12} and folate. A variety of mechanisms might predispose to thiamine deficiency and WKS in cancer. Given the high frequency of residual morbidity, studies should focus on decreasing diagnostic and treatment delay.

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INTRODUCTION

Background

Wernicke-Korsakoff Syndrome (WKS) is a neuropsychiatric syndrome associated with thiamine (vitamin B_1) deficiency (TD).[1] Thiamine is a cofactor for enzymes involved in energy production throughout the body including within muscle, hepatocytes, and neurons. Thiamine must be acquired from the diet, and owing to its high rate of turnover,[2] daily intake is needed to maintain homeostasis. In healthy individuals the body stores up to 2–3 weeks necessity of thiamine, thereby adding a small buffer against disruption in thiamine homeostasis. Such disruption occurs under conditions causing any combination of decreased thiamine availability, accelerated usage, impaired functioning, or excessive loss of thiamine.[3] Decreased availability occurs during starvation, malnutrition, malabsorption, and vomiting.[3] Accelerated thiamine usage occurs in hypermetabolic states, such as during alcohol withdrawal, seizures, infections, critical illness, with fast-growing tumors, diabetes, or following glucose or dextrose loading.[3] Impaired use of thiamine occurs through the direct inactivating effects of certain medications, including metronidazole and fluorouracil, which have been proposed as risk factors for nonalcoholic WKS.[4–7] Finally, excessive loss leading to TD has been reported in diabetes,[8] hemodialysis,[9] and with diuretic use.[10]

Pathophysiology

When TD is severe enough, cells lose their ability to produce aerobic energy and cause buildup of lactic acid and reactive oxygen species.[11] Within a matter of days, cell death begins. In the brain, this pathophysiologic process leads to characteristic neuroanatomic lesions in the medial thalami, mammillary bodies, tectal plate, periaqueductal area of the midbrain, and periventricular regions of the third ventricle, though atypical findings in the cerebral cortex, cerebellum, and cranial nerve nuclei have also been described.[12] When this disease process leads to an observable, clinical syndrome, it is referred to as the WKS. Although historically believed to be 2 separate entities, WKS is now considered to be a single syndrome with a single pathophysiologic mechanism and variable phenomenology.[13] Genetic variations of thiamine transporters have been proposed as an explanation for why TD leads to full-blown WKS in some individuals and not others.[14]

Clinical Factors

Clinically, WKS manifests with 1 or several cognitive, cerebellar, or ocular findings, thus making it relevant to both neurology and psychiatry consultants. The prevalence is up to 2% among the general population[15] and up to 12.5% among patients with alcohol use disorders.[16] The notion of Wernicke's classic triad (confusion, ataxia, and nystagmus) as a reliable diagnostic tool has been refuted[3] as it is present in only 16% of cases.[17] By using the operational criteria proposed by Caine et al.,[18] diagnostic sensitivity increases to 85%, and a diagnosis can be made when patients have any 2 of the following 4 features: nutritional deficiency; ocular signs; cerebellar signs; either altered mental status or mild memory impairment. MRI is costly and lacks sufficient sensitivity to be a reliable diagnostic tool.[19] Still, MRI can confirm suspected WKS owing to its high specificity, and it can rule out other intracranial pathology. Serum thiamine concentration can identify TD and point toward an overall nutritional deficiency but cannot be used alone to diagnose WKS, which is

a clinical syndrome. In addition, the laboratory test is not readily available in most hospitals.[20] Treatment consists of high-dose parenteral thiamine supplementation, which is safe, cheap, and effective when initiated early.[21] Unfortunately, WKS is often under-recognized, and up to 80% of cases are missed.[22] When not treated early and adequately, the downstream effects can include long-term and irreversible cognitive dysfunction, high costs of morbidity, and death.[23]

WKS in Cancer

Owing to historic factors, WKS has been studied mostly in patients with alcohol use disorders. This is changing, however, and an increasingly large body of literature is being published on nonalcoholic WKS among medical and surgical patient populations.[13] Cancer predisposes to TD through the same pathophysiologic mechanisms described earlier (decreased availability, accelerated usage, impaired functioning, and excessive losses). Higher rates of TD among patients with cancer have been reported in several small studies.[5,24] WKS has also been reported in cancer. The prevalence of WKS in patients who died following bone marrow transplants has been estimated in 2 studies, with estimates ranging from 6–33%.[25,26] The remainder of the literature on nonalcoholic WKS in cancer consists of case reports and small case series.[27,28]

The aim of this study is to report on 18 cases of nonalcoholic WKS in patients with cancer who were admitted to an acute care cancer hospital. Our goal was to address the gaps in the literature by describing the demographics, risk factors, clinical manifestations, treatment, and outcomes of patients with nonalcoholic WKS due to cancer.

METHODS

Setting and Study Design

This study was designed as a retrospective chart review and took place at Memorial Sloan Kettering Cancer Center, a large, academic, freestanding cancer hospital in an urban center. A convenience sample was identified as part of routine clinical care provided by the consultation psychiatry service. The sample consisted of adult inpatients referred to the consultation-liaison psychiatry service between July 1, 2013 and December 1, 2014. Patients were evaluated by psychosomatic medicine psychiatry fellows and attending psycho-oncologists during routine care. Patients were included in the study if they were diagnosed with WKS by operationalized criteria and had at least one of the following supporting features: positive findings on MRI; abnormally low serum thiamine concentration; and clinical improvement temporally linked to thiamine repletion. We chose to require a supporting feature to increase diagnostic accuracy as our patient population had multiple comorbidities potentially contributing to altered mental status. Any patient whose clinical presentation was better explained by other etiologies was excluded from the study. Patients with current alcohol use disorders were excluded. The study was exempt from full institutional review, and was approved by our hospital's institutional review board. In a previous case report, 3 patients (case 3, 9, and 11) were described in greater detail.[27]

Data Abstraction

Unblinded data were abstracted from electronic medical records (EMR) by one of the authors (E. I. G.). A standardized abstraction form was used. Cancer staging systems documented in the EMR included American Joint Commission on Cancer for solid tumors other than ovarian, Féderation Internationale de Gynécologie et d'Obstétrique for ovarian cancer, International Staging System for multiple myeloma, Cotswald for Hodgkin lymphoma, and National Cancer Institute for non-Hodgkin lymphomas. When formal staging was not reported in the EMR, data on the presence or absence of metastases were abstracted instead. Current treatment was arbitrarily defined as receiving chemotherapy, surgery, or radiation within the previous 2 months. Weight loss was defined as less than 95% of usual body weight at the time of consultation. Risk factors related to decreased thiamine availability (low oral intake, low appetite, nausea, vomiting, diarrhea, and oral thrush) were considered positive if present for at least 2 weeks at the time of consultation. Risk factors related to accelerated thiamine usage were considered positive if present within the week before diagnosis for corticosteroid administration, evidence of infection, fever, lactic acidosis, elevated lactate dehydrogenase, and glucose infusion, or within the month before diagnosis for sepsis. Elevated heart rate was defined as having an average heart rate greater than or equal to 90 beats per minute in the week before diagnosis. Current metronidazole use was considered positive if the patient received the medication within the week before diagnosis. All medical comorbidities were abstracted from the diagnosis list in the EMR.

Symptoms were abstracted from the chart by reviewing consultation and progress notes. Notes were reviewed for cognitive signs and symptoms including confusion; altered mental status; delirium; hypermotoric or hyperarousal symptoms (e.g., restlessness, agitation, and insomnia); hypomotoric or hypoarousal symptoms (e.g., drowsy, sleepy, lethargic, obtunded, stupor, and hypoactive); memory impairment; attention or concentration impairment; and disorientation. Ocular signs included ophthalmoplegia, nystagmus, and pupillary abnormalities. Cerebellar signs included dysdiadochokinesia, impaired rapid alternating movements, unsteadiness, and ataxia. Other signs included dysarthria, apathy, depression, and mood lability. Psychiatric notes alone were used to detect level of orientation (between 3 and 10 points of orientation); short-term memory deficits (based on 3-word registration and recall at 3 min); attention impairment (based on a digit span test of up to 5 digits forward and 4 digits backward, testing the months of the year in reverse, or spelling "world" in reverse); disorganized thinking (based on clinical interview); and hallucinations (based on clinical interview). The time course of symptom resolution was indicated whenever sufficient information existed. Symptoms were considered resolved on the date of the first note in which symptom resolution was documented. Symptoms not recorded as having resolved at the last pertinent EMR entry were considered unresolved. Follow-up time was number of days between symptom onset and the last pertinent EMR note.

Additional Data

Serum thiamine concentrations were measured at an outside laboratory (Quest Diagnostics Nichols Institute, San Juan Capistrano, CA) as per routine clinical care. The reference range is 8–30 nmol/l and concentrations less than 7 nmol/L are recorded as "abnormally low." Neuroimaging was interpreted by attending neuroradiologists as part of routine clinical care,

and reinterpreted by a neuroradiologist (V. H.) with expertise in WKS for the purposes of this study. Nutritional risk was assessed based on an institution-specific protocol. All inpatients are screened by a registered nurse on admission, and are stratified into low, moderate, or high risk based on predetermined criteria (greater than 10-lb weight loss within the last 3 months; greater than 2-week history of loss of appetite, difficulty chewing or swallowing, nausea, vomiting, diarrhea, or stomatitis; and pregnant or lactating). Based on the risk status, patients then receive a complete assessment by a registered dietician within 24–48 hours (for moderate and high risk) or within 6 days (for low risk).

Data Analysis

All analyses were conducted using Microsoft Excel 2007. Descriptive statistics (means, standard deviations, frequencies, and percentages) were calculated for demographic and medical variables, associated risk factors/clinical features, and clinical manifestations. Descriptive data were used to examine potential risk factors associated with developing WKS. Finally, descriptive statistics were run to examine the potential delay in treatment of WKS.

RESULTS

Demographics

Of the 34 total patients initially identified for potential inclusion, 16 were excluded owing to lack of supporting evidence or the presence of a likelier etiology of clinical presentation, leaving 18 patients for inclusion in the study. The median age was 65 years (mean: 64.2, range: 31–80, and standard deviation 12.54) and 33% were women. Solid tumors were present in 11 cases (61%) and hematologic malignancies in 7 cases (39%). Current treatment consisted of chemotherapy (n = 13; 72%), targeted therapy (n = 3; 17%), surgery (n = 6; 33%), and radiation (n = 4; 22%). Half of the patients (case 1, 3, 4, 5, 9, 11, 13, 15, and 17) died within a year following consultation. Among them, 7 patients (78%) died within the first month following consultation. Other patient characteristics are listed in Table 1.

Risk Factors

Potential risk factors are listed in Table 2. All cases (n = 18; 100%) had at least 1 risk factor associated with decreased thiamine availability. Nearly all patients (n = 17; 94%) had factors associated with accelerated thiamine usage. Medication associated with impaired use of thiamine was documented in 6 cases (33.3%). Factors leading to excessive loss of thiamine were documented in 6 cases (33.3%).

Associated Features

Serum thiamine concentration was measured in 16 patients (89%) and in all cases (n = 16; 100%) was abnormally low (<7 nmol/L). Thiamine concentration was not ordered for case 2, and the sample could not be tested for case 3 owing to collection error. Vitamin B_{12} concentration was measured in 15 patients (83%) and none had deficiency. Folate concentration was measured in 13 patients (72%) and only 1 (8%) revealed deficiency (<3.4 ng/mL). Brain MRI was performed in 10 patients (56%), of which cases 2, 11, and 14 (n = 3; 30%) had typical WE findings. Case 2 had abnormal and symmetric FLAIR (fluid

attenuation inversion recovery) signal hyper-intensities in the mamillary bodies, medial thalami, and periaqueductal area of the midbrain, as well as atypical findings in the medulla. Case 11 had abnormal FLAIR signal hyperintensities in the medial thalami and periaqueductal area. Case 14 had abnormal FLAIR hyper-intensities in the periaqueductal gray. Laboratory investigations and other test results are listed in Supplemental Tables S1 and S2.

Phenomenology

Clinical manifestations are listed in Table 3. Grouped according to the symptom domain, the most common findings included cognitive signs and symptoms (n = 18, 100%), cerebellar signs and symptoms (n = 7, 39%), and ocular signs and symptoms (n = 3, 17%). Ocular findings were among the earliest presenting symptoms in all 3 cases. All patients (n = 18, 100%) had evidence of both nutritional deficiency and altered mental status, satisfying the minimum number of features required to diagnose WKS by operational criteria. Only cases 1 and 4 (n = 2, 11%) presented with all 3 features of Wernicke's triad.

Diagnostic Delay and Treatment

Treatment delay was calculated as the number of days between symptom onset and initiation of treatment. Only cases 8 and 17 did not have sufficient information documented to calculate treatment delay. The average delay was 18 days (range: 2–58 and standard deviation: 18). All patients were administered intravenous (IV) thiamine 500 mg 3 times daily from the onset of treatment, except for 3 cases: case 3, 4, and 14 were initially treated with IV thiamine 100 mg once daily for 3 days, 2 days, and 2 days, respectively; they did not demonstrate signs of improvement until switched to IV thiamine 500 mg 3 times daily.

Symptom Resolution

Symptom resolution is listed in Table 4. Only 3 cases (17%) showed complete resolution of symptoms, and the remaining 15 (83%) had residual symptoms at the time of last follow-up.

DISCUSSION

Our study revealed several important findings about the risk factors, associated features, phenomenology, diagnostic and treatment delay, and symptom resolution in nonalcoholic WKS in cancer.

Risk Factors

Risk factors were grouped according to the mechanism of TD. The 2 most common mechanisms were decreased thiamine availability (as seen in starvation, malabsorption, or vomiting) and accelerated thiamine usage (as seen in hypermetabolic states, physiologic stress, or high cell turnover). This is not surprising given that these features are common among inpatients with cancer. Based on our findings, gastrointestinal tract and hematologic malignancies were the most common cancers, which is consistent with the primary mechanisms by which each cancer type induces TD (decreased absorption and accelerated usage, respectively). Still, some patients had other cancer types, such as gynecologic and skin cancers, serving as a reminder that other risk factors may contribute to WKS. These

other risk factors might include low oral intake or low appetite (whether secondary to tumor burden or chemotherapy), as well as hypermetabolic states seen in infections, systemic illness, or following the stress of surgery and radiation.

Associated Features

Certain additional clinical factors were unexpected. First, a few patients were underweight ($n = 4$, 22%) and many were indeed overweight ($n = 8$, 44%). Next, vitamin B_{12} and folate concentrations were normal in almost all cases ordered. Thus, clinicians should not rule out WKS in patients with cancer who appear to have normal weight or overweight, or for whom other vitamin concentrations are within reference ranges. The fact that thiamine was abnormally low even when other B-vitamin concentrations were normal may reflect the body's relatively low thiamine reserves and its high rate of turnover, both of which may be exaggerated in cancer. Although vitamin supplementation could theoretically have masked an underlying vitamin deficiency, none of the patients whose vitamin B_{12} and folate concentrations had been measured were receiving B_{12} or folate supplements either while admitted or before admission.

Phenomenology

From a phenomenological perspective, in most cases, the clinical manifestation of WKS had no trademarks to distinguish it from delirium by other causes. The most common manifestations were cognitive, with altered level of alertness, inattention, short-term memory impairment, and disorientation comprising the most common features in descending order of frequency. Cerebellar signs were present in slightly less than half of the samples, and ocular findings in a few. The preponderance of patients with only cognitive signs contrasts with those frequently reported in the nonalcoholic WKS literature—that is, patients with the full spectrum of clinical signs.[13] Scalzo et al. suggest that clinicians may have higher thresholds for diagnosing WKS in nonalcoholic patient populations,[13] which may account for the tendency to report patients displaying the full spectrum of signs. Additionally, using the operational criteria, fewer features are required to diagnose nonalcoholic WKS. This may result in overdiagnosis, which, in this patient population, is favorable. Under-reporting or failure to document ocular and cerebellar signs may also account for the preponderance of patients with cognitive symptoms only. Other findings were noted in our sample, including dysarthria, which was present in a small but not insignificant number of patients. Furthermore, wide variation in the earliest symptoms documented made it difficult to discern any temporal pattern to the onset of symptoms.

Diagnostic and Treatment Delay

Diagnostic delay was common, which is consistent with the literature. Many patients had undergone testing that did not lead to diagnosis, some of which was costly, time consuming, and invasive (e.g., lumbar puncture). Thus, nearly all patients had a lag time between symptom onset and initiation of treatment, as high as 58 days in a case. Furthermore, none of the cases were diagnosed before requesting psychiatric consultation, implying that clinicians may not be vigilant about diagnosing WKS in nonalcoholic populations. Because only 2 cases (11%) had all features of the classic triad, our study serves as a reminder that Wernicke's classic triad is not a reliable diagnostic tool. Instead, the operationalized criteria

features for diagnosing Wernicke encephalopathy, proposed by Caine et al.,[18] were present in all cases.

Symptom Resolution

Our findings shed light on the course of illness of nonalcoholic WKS in patients with cancer. The median follow-up time was 20 days (range: 1–427). Complete symptom resolution occurred in only a minority of cases, and most patients had residual cognitive symptoms. Short-term memory deficits were the most common followed by inattention and disorientation. Of the symptoms that resolved, the time course of symptom resolution was variable, which may relate to 2 factors. First, diagnostic and treatment delay varied widely among patients. Second, follow-up examinations did not necessarily occur at standardized time points, which may result in inflated estimates of time to symptom resolution. Still, the fact that residual symptoms were frequent is troubling given that WKS is treatable when detected early.

TREATMENT RECOMMENDATIONS

Currently, there is conflicting and insufficient evidence to guide the use of routine thiamine supplementation for all patients with cancer. As noted in a 2013, review by Luong and Nguyen,[29] thiamine has been reported in preclinical studies as having tumor-promoting properties in some instances and antitumor properties in others. The evidence is much clearer for using thiamine in patients with cancer with suspected or confirmed WKS given the high morbidity and mortality of WKS, the low cost of thiamine, and its excellent safety profile. Therefore, we recommend treating suspected WKS empirically with high-dose IV thiamine based on either the European guidelines (200 mg IV t.i.d. until symptom improvement ceases)[30] or the UK guidelines[1] (500 mg IV t.i.d. for 3 days or longer), although there is insufficient evidence to recommend one dosing strategy vs the other.

Inpatients with cancer remain a vulnerable population with many additional risk factors for TD and WKS conferred. Thus, it is imperative that future studies help guide recommendations for or against the use of prophylactic thiamine administration for the prevention of WKS among patients with cancer admitted to hospital.

Limitations

The study has several limitations. First, the sample is drawn from patients referred to a consultation-liaison psychiatry service, and lacking a random sample may limit generalizability to other patient populations. Psychiatric consultations were likely requested when patients manifested behavioral or cognitive symptoms, potentially leading to an overestimate of cognitive symptoms; however, similarly high prevalence of cognitive symptoms among nonalcoholic patients with WKS has been reported.[13] Second, the retrospective design prevented establishing causality between the associated clinical factors and the development of WKS. Thirdly, the chart review methodology conferred bias in several ways. The data abstraction was not blinded and no independent review was performed. As the chart review relied on EMR, bias relating to documentation of symptoms may have been introduced whether through under-reporting, recall bias at the time of note

writing, or through copying information forward from previous notes. Issues relating to delays in note writing and electronic time stamping of notes may have introduced bias relating to the time course of treatment delay and symptom resolution. Finally, we did not collect data on the use of diuretics in our sample. Given that diuretic use is associated with TD and given that diuretics may be commonly used in patients with cancer,[31] future studies should explore the role of diuretics as potential risk factors for TD and WKS in patients with cancer.

CONCLUSION

This study drew on a real-world sample of patients encountered during routine clinical care provided by an inpatient psychiatric consultation service at a large cancer center. Our findings support the previous work on nonalcoholic WKS demonstrating the predominance of cognitive symptoms, low validity of the classic triad, and significant diagnostic and treatment delay. This study serves as an important foundation on which to direct future work, including validating diagnostic tools and other initiatives to improve early detection, as well as long-term treatment and followup studies.

In summary, nonalcoholic WKS in cancer should be diagnosed early using operational criteria. Although measuring serum thiamine concentration can detect TD, WKS remains a clinical diagnosis. Understanding how cancer and cancer treatments predispose to TD is critical in making a diagnosis. Because cancer confers such risk for TD, we recommend administering high-dose parenteral thiamine for all inpatients with cancer presenting with altered mental status.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

APPENDIX A. SUPPLEMENTARY INFORMATION

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.psym.2015.10.001.

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TABLE 1

Patient Demographics and Clinical Characteristics

Patient no./sex/age	Cancer (site or subtype)	Stage*	Current treatments	Medical comorbidities	Length of stay (days)	Oral vitamins prescribed	Number of risk factors for delirium
1/M/78	Hairy cell leukemia	ND	Targeted therapy, surgery	HTN, AF	40	MVT	3
2/F/46	AML (M2)	ND	Chemo, radiation	ND	112	Folate, Vit D	2
3/M/80	Squamous cell (eyelid)	Met	Radiation	DM_2, HLD, HTN, CAD	31	ND	4
4/F/64	Transitional cell (renal pelvis)	4	Chemo, radiation, surgery	HLD, HTN, PUD	23	Vit D	5
5/M/61	Adenocarcinoma (colon)	4	Chemo, surgery	HTN	14	Vit D, MVT	3
6/M/79	Cholangiocarcinoma	4	Chemo	HTN	14	Vit D, Vit B_{12}	3
7/M/59	PEComa (retroperitoneal)	Met	Targeted therapy	HTN, HLD, AF	5	MVT	1
8/M/66	Multiple Myeloma	3	Chemo, HSCT	HTN, DM_2, CAD, CKD, CHF	37	B-Complex	2
9/M/68	Adenocarcinoma (colon)	4	Chemo	DM_2, HLD, CAD	19	ND	2
10/F/65	Leiomyosarcoma (uterus)	Met	Surgery	OP	20	ND	1
11/F/61	HL (nodular sclerosing)	3	Targeted therapy	CHF, HIV, HLD, AF, OP, HTN, COPD	34	Folate, Vit B_{12}	3
12/M/78	Squamous cell (anus)	4	Chemo, radiation, surgery	AF, CAD, LD	36	ND	2
13/M/70	Burkitt lymphoma	4	Chemo, surgery	DM_2, HTN, HLD, AF	91	ND	3
14/M/31	ATLL		Chemo	HLD	75	ND	3
15/M/63	NSCLC	4	Chemo	HLD, COPD, ARH	3	MVT	1
16/F/49	Adenocarcinoma (ovaries)	3c	Chemo	HLD, HTN, PUD	7	ND	1
17/M/65	Adenocarcinoma (pancreas)	4	Chemo	HLD, HTN,	6	ND	1
18/F/72	DLBCL	4	Chemo	OP, ARH	7	ND	1

M = male; F = female; AML = acute myeloblastic leukemia; PEComa = perivascular epithelioid cell tumor; HL = Hodgkin lymphoma; ATLL = adult T-cell leukemia/lymphoma; NSCLC = non–small cell lung cancer; DLBCL = diffuse large B-cell lymphoma; Chemo = chemotherapy; HTN = hypertension; AF = atrial fibrillation; DM_2 = type 2 diabetes; HLD = hyperlipidemia; CAD = coronary artery disease; PUD = peptic ulcer disease; CKD = chronic kidney disease; CHF = congestive heart failure; OP = osteoporosis; HIV = human immunodeficiency virus; COPD = chronic obstructive pulmonary disease; LD = liver disease, ARH arrhythmia; MVT = multivitamin; Vit D = vitamin D; Vit B_{12} = vitamin B_{12}; B-complex = vitamin B-complex; ND = not documented in the chart.

*For solid tumors, where formal staging was not performed, the presence of metastases is indicated by “Met.”

TABLE 2

Presence or Absence of Risk Factors and Other Associated Clinical Features

Risk factors, grouped by corresponding mechanism leading to thiamine deficiency	Case no.																		Frequency, *n* (%)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
Decreased availability of thiamine																			
Low oral intake, low appetite	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	18 (100)
<95% Usual body weight	+	+		+	+	+	+		+	+		+	+		+	+	+		13 (72.2)
Nausea, vomiting, or diarrhea		+						+	+		+	+	+	+	+	+	+		10 (55.6)
Body mass index <18.5					+							+		+		+			4 (22.2)
Intestinal obstruction											+						+		2 (11.1)
Oral thrush						+													1 (5.6)
Accelerated usage/hypermetabolic state																			
Heart rate ≥90 BPM	+	+		+	+	+		+	+	+	+	+		+	+	+	+	+	15 (83.3)
Corticosteroids	+	+	+	+	+			+					+	+				+	9 (50)
Current infection	+	+	+			+		+	+		+		+	+					9 (50)
Lactic acidosis	+	+	+	+		+		+			+		+						8 (44.4)
Elevated LDH	+				+	+		+						+	+			+	7 (38.9)
Fever	+	+		+				+			+		+						6 (33.3)
Glucose infusion		+	+								+					+		+	5 (27.8)
Sepsis		+						+					+						3 (16.7)
Impaired use of thiamine																			
Fluorouracil *					+	+			+			+					+		5 (27.8)
Metronidazole									+		+								2 (11.1)
Excess loss of thiamine																			
Diabetes			+					+	+				+						4 (22.2)
Renal disease			+				+	+			+								4 (22.2)

+ = Presence of risk factor at the time of diagnosis; BMP = beats per minute; LDH = lactate dehydrogenase.

* Fluorouracil or related chemotherapies (floxuridine and capecitabine).

TABLE 3

Presence or Absence of Signs and Symptoms

Signs and symptoms	Case																		Frequency, *n* (%)
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
Ocular signs																			
Blurry vision	+	+		+															3 (16.7)
Cerebellar signs																			
Unsteadiness	+		+		+				+										4 (22.2)
Impaired coordination				+			+												2 (11.1)
Ataxic gait						+													1 (5.6)
Impaired RAM							+												1 (5.6)
Cognitive symptoms																			
Change in level of alertness	+	+	+	+	+	+	+	+	+	+	+		+		+	+	+	+	16 (88.9)
Attention impairment	+	+	+	+	+	+	+		+	+		+	+	+	+		+	+	15 (83.3)
STM impairment	+		+	+	+	+	+	+		+		+	+		+		+	+	13 (72.2)
Disorientation	+	+		+	+	+		+	+	+	+		+		+	+			12 (66.7)
“Confusion”		+		+	+	+			+	+	+		+		+	+		+	11 (61.1)
Sleep-wake disturbance					+	+			+	+	+						+		7 (38.9)
Disorganized thinking		+			+	+	+		+									+	6 (33.3)
Hallucinations		+		+							+		+						4 (22.2)
Other signs																			
Low energy/weakness	+	+	+		+		+		+			+	+	+	+	+			11 (61.1)
Apathy/depression	+	+	+											+					4 (22.2)
Mood lability	+	+								+								+	4 (22.2)
Dysarthria						+	+		+										3 (16.7)

+ = Presence of a sign or symptom; RAM = rapid alternating movements; STM = short-term memory.

TABLE 4

Number of Days from Onset of Treatment to Symptom Resolution*

Signs or symptoms	Case																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Ocular																		
Blurry vision	3	3		NR														
Cerebellar																		
Unsteadiness	NR	NR							NR									
Cognitive																		
“Confusion”		17		NR	2	2			NR	4	NR		13		1	1		2
Change in level of alertness	2	8	1	4	2	2	3	3	4	4	10		6		1	1	4	1
Sleep-wake reversal						2			NR	4	NR		6				4	
Disorientation	NR	17		NR	2	2	3	3	NR	4	12		NR		NR	1		
STM impairment	NR	NR		NR	NR	NR	NR	3		NR		NR	NR		NR		NR	NR
Attention impairment	NR	NR	1	NR	NR	NR	3			NR		7	6	NR	1		4	20
Disorganized thinking		17			2	2	3		NR									20
“Other”																		
Dysarthria						2	3		3									
Apathy/depression	2	10	2											6				
Mood lability	2	10								4								2
Follow-up period (days)	52	393	2	16	13	11	41	3	6	44	12	298	186	70	24	3	4	427

NR = no resolution.

*Empty cells indicate that patient did not exhibit sign or symptom; therefore data on symptom resolution are not applicable in these cases.