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Association between malignancy and non-alcoholic Wernicke's encephalopathy: a case report and literature review

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Background. Wernicke's encephalopathy is a serious medical condition associated with high morbidity and mortality caused by deficiency of thiamine. This disease is classically associated with alcoholism, but is underappreciated in the nonalcoholic population. There is growing acknowledgement of the development of Wernicke's encephalopathy in patients with malignancies.

Methods. We conducted a literature review in PubMed for cases of Wernicke's encephalopathy occurring in patients with malignancy. We also present the case of a 47-year-old woman with recurrent laryngeal cancer and multiple hospital admissions for malnutrition. Neurological examination was notable for pendular nystagmus, severe gait ataxia, confusion, and poor memory consolidation. MRI of the brain was significant for T2-weighted fluid-attenuated inversion recovery hyperintensities in periaqueductal regions, medial thalami, and the tectal plate, typical for Wernicke's encephalopathy. She was treated with thiamine repletion, and had marked improvement in her mental status and some improvement in her vision problems and ataxia, although some nystagmus and significant short-term memory impairment persisted.

Results. The literature review yielded dozens of case reports of Wernicke's encephalopathy in patients with malignancy, dominated by cases of patients with malignancies of the gastrointestinal system, followed by those with hematologic malignancies.

Conclusions. Malignancy is an important risk factor for the development of Wernicke's encephalopathy. This diagnosis is underappreciated and difficult for the clinician to discern from multifactorial delirium. Clinicians should be aware to treat at-risk patients with thiamine immediately, especially if multiple risk factors are present.

Keywords: cancer, encephalopathy, malignancy, non-alcoholic, Wernicke's.

Vitamin B1, also known as thiamine, is utilized by neurons in several essential biochemical pathways including those of carbohydrate metabolism, lipid metabolism, and production of amino acids and neurotransmitters.[1] At the cellular level, thiamine is converted into thiamine pyrophosphate, which acts as a co-factor for the enzymes α-ketoglutarate-dehydrogenase and pyruvate-dehydrogenase in the citric acid cycle, as well as the enzyme transketolase in the pentose phosphate pathway of energy metabolism.[1] A deficiency of thiamine may lead to oxidative stress, which produces focal accumulation of lactic acid, free radicals, and cytokines, ultimately leading to neuronal death by apoptosis and necrosis.[1] This neuronal damage can occur in the periphery, causing a neuropathy commonly known as Beriberi. In the central nervous system, neurons in the periaqueductal gray matter, medial thalami, and mamillary bodies have demonstrated high utilization and turnover of thiamine and glucose, and are particularly prone to damage in instances of thiamine deficiency, producing a syndrome commonly known as Wernicke's encephalopathy.[1]

Wernicke's encephalopathy and its complication, Korsakoff's amnestic syndrome, are well known complications of chronic alcohol abuse.[2] Wernicke's encephalopathy is characterized by the triad of confusion, ophthalmoplegia, and gait ataxia. Korsakoff's syndrome is the result of advanced Wernicke's encephalopathy and is characterized by memory impairment and confabulation. Wernicke's encephalopathy has serious sequelae if untreated and is associated with high risk of morbidity and mortality.[2] While Wernicke's encephalopathy can be treated and reversed, Korsakoff's syndrome is, unfortunately, a permanent condition. Untreated Wernicke's encephalopathy can also lead to coma and eventually death.[2]

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Alcoholics are typically deficient in thiamine due to a combination of poor dietary intake, gastric malabsorption, and impaired hepatic storage.[3] Alcoholism is a major risk factor for the development of Wernicke's encephalopathy, and alcoholics comprise the majority of cases, which is estimated to be anywhere from 60% to 75% of diagnoses.[4] In addition, according to one study, 12.5% of noted alcohol abusers were found to have evidence of Wernicke's encephalopathy at autopsy, which suggests that Wernicke's encephalopathy is currently underdiagnosed in this population.[2]

While Wernicke's encephalopathy is usually a disease associated with alcoholism, it is often underappreciated in nonalcoholics, who may develop thiamine deficiency through other means. Severe malnutrition can cause thiamine deficiency through obvious mechanisms of poor dietary intake.[5] HIV infection and other systemic disorders can induce thiamine deficiency by increasing the basal metabolic rate.[6–8] It has been suggested that thiamine may be lost in hemodialysis.[9–11]

There is a growing appreciation of Wernicke's encephalopathy in patients with malignancies. Patients with malignancies, as patients with other systemic disorders, have increased basal metabolic rates, which may induce depletion of thiamine. Malignancies of the gastrointestinal system have been particularly associated with the development of Wernicke's encephalopathy, believed to be due to the added mechanisms of impaired absorption, especially when compounded by intervention such as resection of parts of the gastrointestinal tract, itself a profound risk factor for thiamine deficiency.[12] The fluoropyrimidine class of chemotherapeutic agents, which includes the agent 5-fluorouracil, has also been associated with the development of Wernicke's encephalopathy by inducing increased thiamine metabolism, placing those with malignancies getting these treatments at further risk.[13,14]

Wernicke's encephalopathy is currently underdiagnosed in the population. This is owed in no small part to the clinical manifestations of the disease, which are often hard to recognize and rarely present as a complete triad. Additionally, those at risk for nonalcoholic Wernicke's encephalopathy often have multiple co-morbid conditions, which can make it difficult for the clinician to discern from multifactorial delirium. Caine's diagnostic criteria has been established as a clinical tool to assess for Wernicke's encephalopathy, which improves the sensitivity of recognizing and diagnosing this disease from 22%, with the classic triad, to 85% (Table 1).[15]

Case Presentation

We present the case of a 47-year-old woman diagnosed with laryngeal cancer 3 years prior to admission, which had been treated with chemotherapy (1 cycle of docetaxel, cisplatin, and 5-fluorouracil [TPF]), radiation therapy, and resection (transoral robotic surgery [TORS] and bilateral neck dissection), but found to have recurred several months prior to admission. Her past medical history is also significant for hypertension and end-stage renal disease for which she receives hemodialysis. She had been recently discharged from our hospital 1 week prior to admission, when she was noted to have severe malnutrition as she was not tolerating oral intake. The severity of her malnutrition was illustrated by her rapid and profound weight loss of 43 kg over the course of 6 months. At that time, she refused percutaneous endoscopic gastrostomy tube placement, but recovered her ability to eat food after speech and laryngeal rehabilitation. She returned to our hospital complaining only of nausea, but appeared acutely ill with delirium, and also appeared malnourished.

Initial evaluation revealed bacteremia and her mental condition improved with antibiotics and supportive therapy. She required a prolonged hospital stay, during which time she began to complain of double vision. Neurological examination at that time was significant for persistent, pendular nystagmus in primary gaze and in all directions, as well as jerky ophthalmologic pursuit and slow saccades. After several weeks, while still in the hospital, she had deterioration in her mental status and again developed acute confusion. She also had a newly ataxic gait and impaired short-term memory and alertness.

She had a full evaluation for infection, which was negative, and she remained afebrile and with normal white blood cell count. Her serology, including basic metabolic panel and complete blood count, were unremarkable. Given her recurrent laryngeal cancer, there was high suspicion for CNS metastases and leptomeningeal disease, but lumbar puncture was normal, with unremarkable cytology and flow cytometry. MRI of her brain revealed T2-weighted fluid-attenuated inversion recovery (FLAIR) hyperintensities in the periaqueductal area, medial thalami, and tectal plate, which is typical for Wernicke's encephalopathy (Figs. 1–4).[16,17]

Given clinical findings and imaging results, she was diagnosed with acute Wernicke's encephalopathy, and she was treated with aggressive thiamine repletion at a dosage of 500 mg intravenously every 8 hours for 5 days. She had immediate improvement in her mental status, became attentive, and was no longer confused. She had persistence, however, of her memory impairment and had poor scoring on recall tasks. There was partial improvement in her nystagmus and ataxia.

She agreed to percutaneous endoscopic gastrostomy tube placement, and was also instructed to take regular, lifetime thiamine supplementation at 100 mg daily via gastric tube. She was discharged to a sub-acute rehab facility, where she regained much of her strength, and was able to ambulate independently for short distances 4 weeks after arrival. She was last seen in our hospital 2 months after discharge, when she was found to have gained 2 kg in body weight.

Table 1. Caine's diagnostic criteria

Sign	Value
Ocular abnormalities	1
Cerebellar abnormalities	1
Confusion or memory impairment	1
History of malnutrition	1

Total values of 2 or higher indicate 85% sensitivity when suspecting Wernicke's encephalopathy.

Literature Review

A literature review was conducted in PubMed. The terms "Wernicke," "Encephalopathy," "Malignancy," "Cancer," and all combinations of those terms were used in our literature search. The review yielded 40 relevant papers and abstracts, largely in the

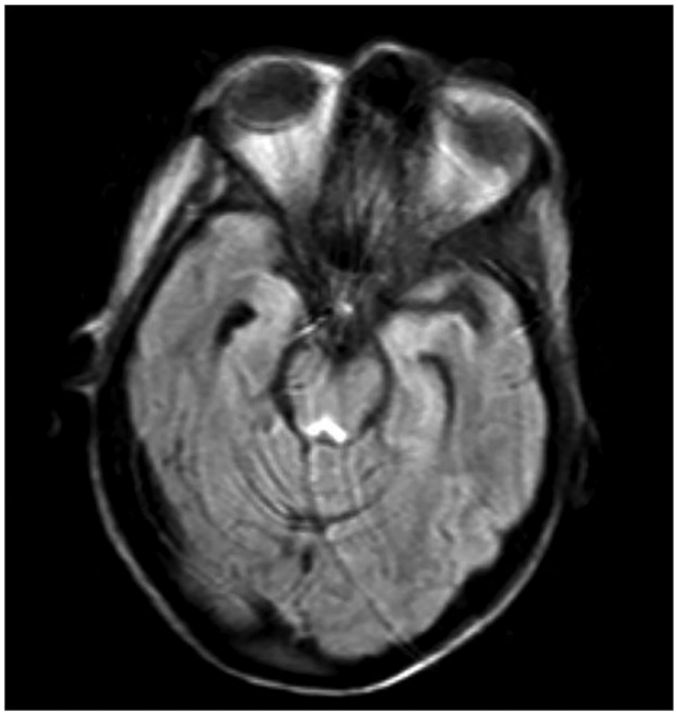

Fig. 1. T2-weighted FLAIR hyperintensity demonstrated in periaqueductal area. Some motion artifact.

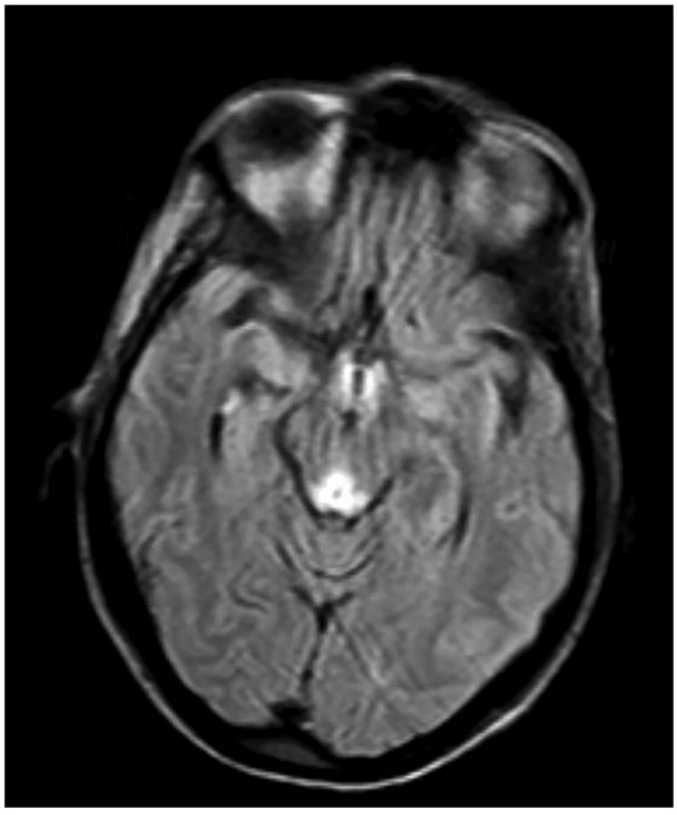

Fig. 2. T2-weighted FLAIR hyperintensities demonstrated in tectal plate, periaqueductal area, and area near mammillary bodies. Some motion artifact.

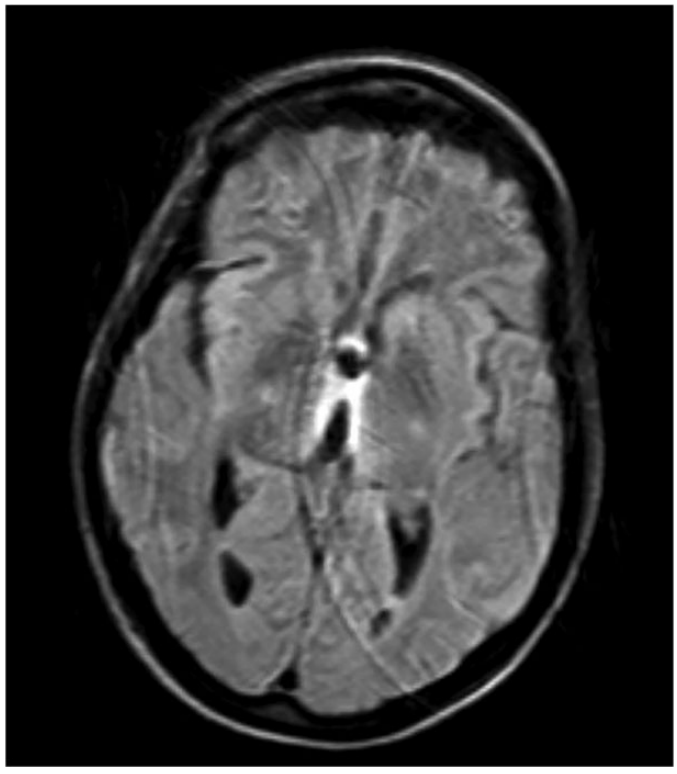

Fig. 3. T2-weighted FLAIR hyperintensities demonstrated in medial thalami and area around third ventricle. Some motion artifact.

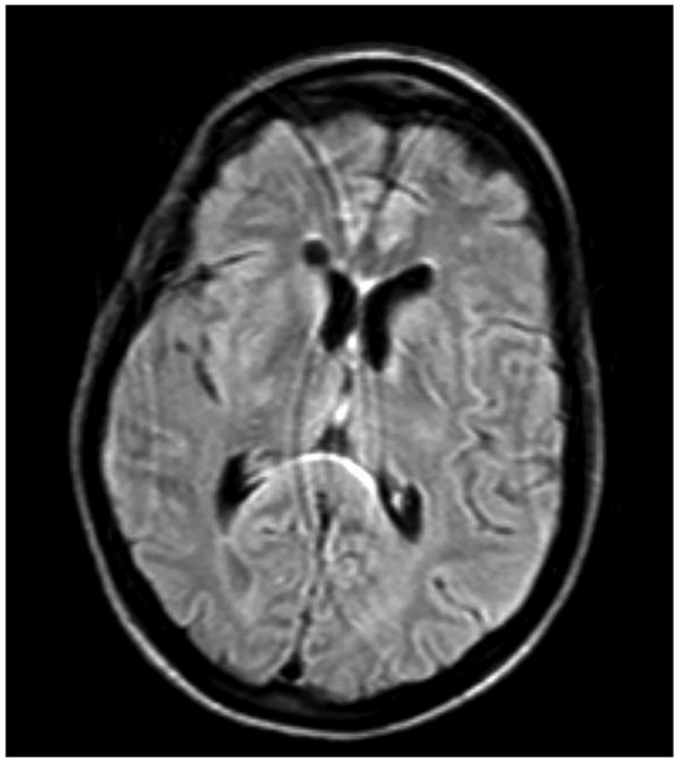

Fig. 4. T2-weighted FLAIR hyperintensity demonstrated in area around third ventricle. Some motion artifact.

Table 2. Results of a literature review in PubMed

Malignancy	Age	Sex	Barriers to Nutrition	Chemotherapeutics	Surgical Interventions	Imaging	Clinical Findings	Outcome	Author, Year, and Citation
Colon cancer	59	Female	Unknown	5-FU, otherwise unknown	Unknown	MRI	Confusion, ataxia (NOS), otherwise unknown	Unknown	Guilloton L. 2005.[19]
Colon cancer	54	Male	Persistent nausea, TPN	Unknown	Colectomy (subtotal)	MRI	Lethargy, inattentiveness, memory impairment, ophthalmoplegia (lateral movements), nystagmus (pendular), ataxia (NOS), muscle stiffness, hyporeflexia	Slight resolution; persistence of all symptoms	Nolli M. 2005.[20]
Colon cancer	56	Female	Ileus, TPN	Unknown	Hemicolectomy (right)	MRI	Lethargy, nystagmus (horizontal), ataxia (limbs), hyporeflexia	Nearly full resolution; persistence of trace nystagmus and ataxia	Pagnan L. 1998.[21]
Colon cancer	56	Female	Unknown	Calcium folinate, 5-FU	Unknown	MRI	Alteration of consciousness, seizures, ophthalmoplegia (NOS), nystagmus (horizontal), hyperreflexia	Nearly full resolution; persistence of trace ataxia	Papila B. 2010.[22]
Gastric cancer	66	Female	Persistent nausea and vomiting, TPN	NOS	Unknown	Unknown	Disorientation, memory impairment	Full resolution	Onishi H. 2004.[23]
Gastric cancer	68	Male	Unknown	Unknown	Gastrectomy (subtotal)	MRI	Memory disturbance, diplopia, ophthalmoplegia (total), ataxia (gait), hyporeflexia	No improvement	Kikuchi A. 2000.[24]
Gastric cancer	48	Male	Alcoholism	Unknown	Gastrectomy (total)	MRI negative	Memory impairment, ophthalmoplegia (bilateral lateral recti), nystagmus (horizonta), ataxia (truncal and gait), areflexia	Improved, NOS	Arai M. 1997.[25]
Gastric cancer	71	Female	Unknown	Unknown	Unknown	MRI	Confusion, memory impairment, nystagmus (horizontal), ataxia (limbs), hyporeflexia	Slight improvement; persistence of all symptoms	Weidauer S. 2004.[26]
Gastric cancer, adenocarcinoma	28	Female	Esophageal stenosis, poor oral intake	5-FU	Unknown	Unknown	Confusion, dizziness, deafness, nystagmus (NOS), deafness, ataxia (gait)	Full resolution	Kondo K. 1996.[13]
Gastric cancer, adenocarcinoma	35	Male	Partial gastric outlet obstruction, vomiting, poor oral intake	Unknown	Unknown	MRI	Confusion, dysarthria, ataxia (gait)	Full resolution	Kudru CU. 2014.[27]

Continued

Table 2. *Continued*

Malignancy	Age	Sex	Barriers to Nutrition	Chemotherapeutics	Surgical Interventions	Imaging	Clinical Findings	Outcome	Author, Year, and Citation
Gastric cancer, signet ring cell	48	Female	Esophagogastric junction obstruction, nausea and vomiting, primarily liquid diet, intermittent parenteral nutrition	Paclitaxel, S-1	Esophagogastric junction stent placement	Unknown	Nystagmus (NOS), ataxia (gait)	Nearly full resolution; persistence of mild nystagmus	Jung ES. 2010.[28]
Gastric cancer, signet ring cell	58	Female	Nausea and vomiting	Oxaliplatin, 5-FU, leucovorin		MRI	Confusion, disorientation, ophthalmoplegia (NOS), ataxia (NOS)	Died from neurological complications	Jung ES. 2010.[28]
Gastric cancer, submucosal	56	Male	Alcoholism	Unknown	Gastrectomy (total)	Unknown	Ophthalmoplegia (bilateral lateral recti), severe ataxia (gait), areflexia	Improved, NOS	Arai M. 1997.[25]
Hepatocellular carcinoma	72	Male	None	None	Hepatic lobectomy	None	Confusion, inattention, memory impairment, insomnia	Full resolution	Onishi H. 2005.[29]
Pancreatic cancer, adenocarcinoma	52	Male	Alcoholism	Unknown	Whipple procedure	MRI	Confusion, memory impairment, ataxia (trunk and gait)	Full resolution	Karayiannakis AJ. 2011.[30]
Pancreatic cancer, neuro-endocrine	45	Female	Recurrent hypoglycemia, persistent nausea and vomiting	Cisplatin, etoposide, streptozotocin, doxorubicin, interferon, somatostatin analogues	Unknown	MRI negative	Confusion, nonreactive pupils, ophthalmoplegia (bilateral lateral recti), ataxia (trunk and gait)	Full resolution	Grunenwald S. 2009.[31]
Rectal cancer	73	Male	Severe nausea, poor oral intake primarily liquid	Unknown	Hemicolectomy (right)	MRI	Diplopia, ophthalmoplegia (left lateral rectus), gait impairment, ataxia (limbs)	Partial resolution; persistence of mild confabulation	Chu K. 2002.[32]

This table summarizes the clinical history, features, and outcomes of case reports of Wernicke's encephalopathy in patients with gastrointestinal system malignancies.
Abbreviations: 5-FU, 5-fluorouracil; NOS, not otherwise specified; TPN, total parenteral nutrition.

Table 3. Results of a literature review in PubMed

Malignancy	Age	Sex	Barriers to nutrition	Chemotherapeutics	Surgical interventions	Imaging	Clinical findings	Outcome	Author, Year, and Citation
Acute leukemia, NOS	15	Female	Unknown	NOS	Unknown	MRI	Lethargy, amnesia, ataxia, occulomotor deficits (NOS)	Full resolution	Vanhulle C. 1997.[33]
ALL	9	Male	Limited oral intake (carbohydrates including soft drinks)	Methotrexate (intrathecal), vincristine, prednisone, cyclophosphamide, adriamycin	None	None	Diffuse weakness, double vision, unsteadiness, alteration of consciousness	Died before complete neurological improvement	Miyajami Y. 1993.[34]
Acute mixed lineage leukemia	12	Male	Nausea, persistent diarrhea, TPN	Cytosine arabinoside, aclarabucin, granulocyte colony stimulating factor	None	MRI	Occulomotor palsy (NOS), nystagmus	Full resolution	Onodera N. 1998.[35]
AML	42	Female	TPN	Cyclosporin A, methotrexate	Allogeneic peripheral blood stem cell transplantation	MRI	Confusion, nystagmus (horizontal), generalized weakness, ataxia (truncal and lower limbs)	Full resolution	Baek JH. 2005.[36]
ALL	16	Male	Acute pancreatitis, vomiting, TPN	Prednisone, L-asparaginase, daunorubicin, vincristine, low-dose cytarabine, 6-mercaptopurine, high-dose methotrexate	None	MRI	Confusion, disorientation, dizziness, vertigo, diplopia.	Full resolution	Muwakkit S. 2009.[37]
ALL	3	Female	Diarrhea, parenteral nutrition	NOS	None	Unknown	Abnormal eye movements	Wernicke's encephalopathy diagnosed at autopsy	Brück W. 1991.[38]
ALL, T-cell	20	Male	Poor oral intake (limited to soft drinks)/6 weeks	None	None	MRI	Confusion	Full resolution	Lacasse L. 2004.[39]
AML	13	Female	Persistent nausea and vomiting	Idarubicin, etoposide, cytarabine	None	MRI	Confusion, nystagmus (NOS), ophthalmoplegia (NOS)	Full resolution	D'Aprile P. 2000.[40]
B-cell lymphoma, diffuse large cell	37	Female	Alcoholism, nausea (with good oral intake)	R-CHOP	Unknown	MRI	Obtunded, disconjugate gaze	Full resolution	Turner JE. 2004.[41]
B-cell lymphoma, high-grade	51	Male	Unknown	Methotrexate, NOS	Unknown	Unknown	Confusion, ophthalmoplegia (bilateral, NOS), nonreactive pupils, ptosis, visual hallucinations	Full resolution. Also treated for new-onset seizures (hallucinations).	Gregory J. 2012.[42]
B-cell lymphoma, Hodgkin's	60	Female	Anorexia, nausea	NOS	Unknown	MRI negative	Disorientation, depression, nystagmus (horizontal), psychomotor retardation proximal weakness, hyporeflexia	Partial resolution; died 2 months later before full recovery	Macleod AD. 2000.[43]

Continued

Table 3. *Continued*

Malignancy	Age	Sex	Barriers to nutrition	Chemotherapeutics	Surgical interventions	Imaging	Clinical findings	Outcome	Author, Year, and Citation
B-cell lymphoma, Non-Hodgkin's	56	Male	Persistent nausea and vomiting	R-CHOP	Gastric biopsy	MRI negative	Vertical nystagmus, ataxia (gait)	Full resolution	Boniol S. 2007.[44]
B-cell lymphona, diffuse large cell	47	Male	Nausea, TPN	R-CHOP	Hemicolectomy (right)	MRI	Confusion, lethargy, hallucinations (visual and auditory)	Slight improvement; died shortly after diagnosis	Lee SM. 2012.[45]
CNS lymphoma, primary	62	Female	Nausea, poor oral intake primarily carbohydrates	High-dose methotrexate, cytarabine	Unknown	MRI	Confusion, memory impairment, ataxia (mild, NOS)	Slight improvement; persistence of confusion and memory impairment	Richardson S. 2010.[46]
Multiple myeloma	50	Female	Nausea and vomiting, poor oral intake	Unknown	Autologous stem cell transplantation	MRI	Confusion, lethargy, inattention, ophthalmoplegia (left lateral rectus), nystagmus (horizontal)	Partial resolution; persistence of memory impairment	Morcos Z. 2004.[47]
Promyelocytic leukemia	32	Female	Parenteral nutrition	Daunorubicin, cytosine arabinoside, 6-mercaptopurine	Unknown	Unknown	Memory impairment	Died; Wernicke's encephalopathy diagnosed at autopsy	Pittella JE. 1990.[48]
T-cell lymphoma, diffuse high-grade large cell (histiocytic)	54	Male	Mucositis causing anorexia, persistent nausea and vomiting	Cyclophosphamide, vincristine, prednisone, bleomycin, doxorubicin, procarbazine	Radiotherapy	None	Confusion, lethargy, memory impairment, nystagmus (horizontal)	Partial resolution; persistence of memory impairment	Engel PA. 1991.[49]

This table summarizes the clinical history, features, and outcomes of case reports of Wernicke's encephalopathy in patients with hematologic malignancies.
Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; NOS, not otherwise specified; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; TPN, total parenteral nutrition.

Table 4. Results of a literature review in PubMed

Malignancy	Age	Sex	Barriers to nutrition	Chemotherapeutics	Surgical interventions	Imaging	Clinical findings	Outcome	Author, Year, and Citation
Adrenal gland cortical carcinoma	70	Female	None	Mitotane, cisplatin, doxorubicin, etoposide	Unknown	None	Disorientation, inattention	Full resolution	Yae S. 2005.[50]
Endometrial adenocarcinoma	57	Female	Unknown	Unknown	Total abdominal hysterectomy and bilateral salpingo-oophorectomy	MRI	Lethargy, memory impairment, nystagmus (all directions)	Partial resolution; persistence of memory impairment	Flint AC. 2006.[51]
Lung cancer	71	Male	Loss of appetite	Unknown	Unknown	Unknown	Confusion, inattention, ataxia (gait)	Full resolution	Onishi H. 2004.[23]
Maxillary cancer	77	Female	Dysphagia	NOS	Radiotherapy	Unknown	Confusion, memory disturbance, nystagmus (horizontal), ataxia (gait)	Full resolution	Onishi H. 2004.[23]
Nasopharyngeal carcinoma	46	Female	Unknown	Cisplatin, 5-FU	Radiotherapy	MRI	Confusion, lethargy, diplopia, headaches	Full resolution	Cho IJ. 2009.[52]
Nasopharyngeal carcinoma	62	Male	Ischemic colitis, diarrhea	Docetaxel	Unknown	MRI	Confusion, nystagmus (NOS), ataxia (NOS)	Died	Kosta P. 2005.[53]
Neuroectodermal tumor, Frontal lobe	12	Male	Mucositis causing anorexia, TPN	Methotrexate, etoposide, cyclophosphamide, carboplatinum	Tumor resection, radiotherapy, autologous peripheral hematopoietic stem cell rescue	MRI	Confusion, hallucinations, tremors (diffuse)	Slight improvement, NOS	Cefalo MG. 2014.[54]
Osteosarcoma	17	Female	Frequent vomiting, parenteral nutrition	Doxorubicin, methotrexate, ifosfamide, cisplatin	Unknown	Unknown	Somnolence, blurry vision, nystagmus (horizontal and vertical), ataxia (trunk and limbs), hyporeflexia	Died; Wernicke's encephalopathy diagnosed at autopsy	Kálmánchey R. 1994.[55]
Peritoneal carcinoma, primary	76	Female	Persistent nausea, TPN	Paclitaxel, carboplatin	Unknown	MRI	Confusion, memory impairment, diplopia, ataxia (NOS)	Partial resolution; peristent confusion and memory impairment	Kim KH. 2013.[56]
Pontine glioma, diffuse intrinsic	6	Male	None	Vinorelbine, nimotuzumab	Unknown	MRI	Restlessness, dysarthria, blurry vision, opthalmoplegia (bilateral lateral recti), ataxia (truncal)	Partial resolution; persistence of occulmotor deficits and ataxia	Cefalo MG. 2014.[54]

Continued

Table 4. *Continued*

Malignancy	Age	Sex	Barriers to nutrition	Chemotherapeutics	Surgical interventions	Imaging	Clinical findings	Outcome	Author, Year, and Citation
Squamous cell carcinoma, tongue	28	Female	Persistent nausea and vomiting	NOS	Partial glossectomy with lateral neck dissection, radiotherapy to neck	Unknown	Confusion, inattention, memory impairment, nystagmus (horizontal gaze-evoked), diffuse weakness, ataxia (NOS), sensory impairment (distal)	Nearly full resolution	Fikhman G. 2011.[57]
Squamous cell carcinoma, tonsil	63	Female	Persistent nausea and vomiting	NOS	Cholecystectomy, radiotherapy to neck	Unknown	Confusion, diplopia, vertigo, ataxia (NOS)	Nearly full resolution; persistence of mild ataxia	Fikhman G. 2011.[57]

This table summarizes the clinical history, features, and outcomes of case reports of Wernicke's encephalopathy in patients with various malignancies.
Abbreviations: 5-FU, 5-fluorouracil; NOS, not otherwise specified; TPN, total parenteral nutrition.

form of case reports, representing 46 total cases of Wernicke's encephalopathy diagnosed in patients with active malignancy. Malignancies of the gastrointestinal system represented 17 of the 46 total case reports (Table 2). Hematologic malignancies also represented 17 of the 46 total case reports (Table 3). The remainder of the case reports included 5 incidences of head and neck malignancies, 2 incidences of primary central nervous system malignancies, and 1 incidence each of gynecological, pulmonary, skeletal, genitourinary, and endocrinological malignancies (Table 4).

Discussion

There is a growing literature base suggesting association between malignancies and the development of Wernicke's encephalopathy. Our literature review chiefly associates gastrointestinal and hematologic malignancies with the development of this condition. Gastrointestinal malignancies are particularly well represented in our literature review because of the many means by which they induce inadequate supply of the vitamin thiamine. This particular patient population is particularly prone to poor nutritional intake, poor nutritional absorption, and increased thiamine utilization through the very nature of their disease. They are also prone to complications such as persistent nausea and vomiting as well as gastrointestinal tract obstruction, which further impair adequate intake of thiamine. These factors may be additionally exacerbated by iatrogenic intervention, such as surgical resection of the gastrointestinal tract, which can expose these patients to further risk of thiamine deficiency.

This phenomenon is not unique to gastrointestinal malignancies, as Wernicke's encephalopathy is also well represented in hematologic malignancies and observed in other malignancies. The many factors described in our discussion of gastrointestinal malignancies are also likely working in tandem to induce thiamine deficiencies in these cases.

The vast majority of case reports describe significant barriers to adequate nutritional intake including persistent nausea and vomiting, anorexia, mucositis, obstruction, and total parenteral nutrition, which patients with malignancies are predisposed to as direct sequelae of their disease processes and their treatments. The clinician should be extra cautious and have high suspicion for thiamine deficiency in cases of significantly poor nutritional intake. There are several case reports of patients with malignancies who do not have any barriers to nutrition or any other known risk factors for developing Wernicke's encephalopathy, which suggests that malignancies are an independent risk factor for developing this disorder.

An overwhelming number of the diagnoses of Wernicke's encephalopathy in our literature review were made at the time of MRI. Given the low sensitivity of MRI in diagnosing Wernicke's encephalopathy (53% by one study[16]), this disease is likely being underdiagnosed and undertreated. Additionally, our literature review reveals that significant time often passes between the initial manifestation of Wernicke's encephalopathy and its diagnosis. Unfortunately, these factors ultimately lead to worse patient outcomes; some patients in our review died from this acute neurological condition, while many others did not achieve full recovery from this eminently treatable disease. These facts also illustrate the difficulty of diagnosing this particular condition in

cancer patients, who often have complex medical histories and disease presentations.

A high clinical suspicion remains the best diagnostic tool for identifying Wernicke's encephalopathy. As above, MRI remains the most prevalent and valuable imaging modality for making a real-time diagnosis of Wernicke's encephalopathy, but while highly specific, this test has a low sensitivity for detection of this disease and is not reliable for making this diagnosis.[16] Thiamine levels can be normal in patients with florid Wernicke's encephalopathy, and there are no other available serological markers to assist the clinician with this diagnosis.[18] Caine's criteria is a useful diagnostic tool for the clinician who suspects a diagnosis of Wernicke's encephalopathy, and its employment vastly increases the sensitivity in detecting this disorder. If Caine's criteria is employed to case presentations in our literature review retrospectively, an early diagnosis of Wernicke's encephalopathy can be made in all but one case. A good understanding of the pathophysiology and epidemiology of Wernicke's encephalopathy, when coupled with the use of Caine's criteria, can further increase the sensitivity of detecting this disease.

Our literature review illustrates the growing association between malignancy and Wernicke's encephalopathy. Consistent with recent literature, Caine's criteria concerns itself only with history of malnutrition, and does not otherwise delineate between alcoholic and nonalcoholic causes.

Once suspected, treatment should be initiated as soon as possible. A recent review reveals that there is currently insufficient evidence from randomized, controlled trials to suggest an optimal dose, route, and duration of thiamine repletion in the treatment of Wernicke's encephalopathy.[1] Existing literature, however, supports the use of thiamine 500 mg intravenously (administered over 30 minutes) or intramuscularly, three times per day for 2 to 3 days; the intravenous and intramuscular routes are used to ensure adequate absorption.[1] Where an effective response is observed, the dosage can be reduced to 250 mg intravenously or intramuscularly daily for 3 to 5 more days, or until no further clinical improvement is seen.[1] The existing literature shows that dosages of 100 to 250 mg daily may be inadequate to improve clinical signs or prevent death.[1] Care should also be taken if patients have a history of malnutrition without any evidence of Wernicke's encephalopathy, and thiamine supplementation should be offered to these patients especially if parenteral administration of nutrition or glucose is being considered.

The patient in our case report illustrates the diagnostic difficulty in a patient with malignancy. She was not an alcoholic, but had several other known risk factors for Wernicke's encephalopathy including malignancy, severe malnutrition, and hemodialysis treatments. She was noted to have alteration of mental status on admission, which was thought to be due to her underlying sepsis as well as her severe nutritional deficiencies; indeed, her mental status was noted to have improved after administration of antibiotics and nutritional support, but slowly deteriorated during her hospital course as she developed acute confusion and inattentiveness, as well as ataxia and nystagmus. There was large concern for recurrent sepsis as well as metastatic or leptomeningeal spread of her malignancy as the cause of her symptomatology. Utilizing Caine's criteria, however, we would have high suspicion for this condition given her nutritional deficits, oculomotor abnormalities, acute confusion, and ataxia (Caine's criteria suggests Wernicke's encephalopathy if satisfying 2 out of the 4 criteria). We would also have had higher suspicion for this disorder in the face of mounting evidence associating this condition with malignancy.

Based on our literature search, our case report may be the first describing Wernicke's encephalopathy in a patient with laryngeal cancer.

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