A Case of Wernicke’s Encephalopathy Following Fluorouracil-based Chemotherapy

The pyrimidine antimetabolite 5-fluorouracil (5-FU) is a chemotherapeutic agent used widely for various tumors. Common side effects of 5-FU are related to its effects on the bone marrow and gastrointestinal epithelium. Neurotoxicity caused by 5-FU is uncommon, although acute and delayed forms have been reported. Wernicke’s encephalopathy is an acute, neuropsychiatric syndrome resulting from thiamine deficiency, and has significant morbidity and mortality. Central nervous system neurotoxicity such as Wernicke’s encephalopathy following chemotherapy with 5-FU has been reported rarely, although it has been suggested that 5-FU can produce adverse neurological effects by causing thiamine deficiency. We report a patient with Wernicke’s encephalopathy, reversible with thiamine therapy, associated with 5-FU-based chemotherapy.

Key Words: Fluorouracil; Wernicke’s Encephalopathy; Thiamine

INTRODUCTION

Neurotoxicity, especially peripheral neuropathy, is a common adverse effect of cytotoxic chemotherapeutic agents, but central nervous system (CNS) toxicity is relatively uncommon. 5-Fluorouracil (5-FU), a fluorinated pyrimidine, is an antineoplastic antimetabolite first introduced in 1958 that is used in the treatment of various solid cancers such as carcinoma of the colon, rectum, breast, stomach, and pancreas (1). This fluorinated pyrimidine is metabolized inside the cells to 5-fluoro-2-deoxyuridine-5-phosphate, which inhibits thymidylate synthase. Blockade of this enzyme inhibits DNA synthesis. Common side effects of 5-FU are related to its effects on the bone marrow (leukopenia) and gastrointestinal epithelium (stomatitis, esophagopharyngitis, diarrhea, anorexia, nausea, vomiting) (2). However, neurotoxicity is uncommon with 5-FU-based chemotherapy (3). Wernicke’s encephalopathy, an acute neuropsychiatric syndrome that results from thiamine deficiency, has rarely been associated with 5-FU treatment. Here, we report a patient who developed imaging-documented Wernicke’s encephalopathy following 5-FU-based chemotherapy and who recovered after stopping therapy.

CASE REPORT

A 46-yr-old woman was diagnosed with nasopharyngeal cancer 5 months before being admitted to our hospital for a course of chemotherapy. She had no history of chronic alcohol consumption or benzodiazepine addiction, or any other significant medical history including malnutrition, surgery or herbal medications. There were no laboratory abnormalities. Concurrent chemoradiation therapy was performed with cisplatin (100 mg/m² at 3-week intervals). One month after the completion of concurrent chemoradiation therapy, we gave her chemotherapy consisting of a continuous infusion of 5-FU 1,000 mg/m²/day for 4 days and cisplatin 75 mg/m² for 1 hr on the first day of each chemotherapy cycle at 3-week intervals. She experienced NCI CTC (v. 3.0) grade 2 stomatitis and grade 3 neutropenia during the first cycle, which resolved after supportive therapy. There was no diarrhea or vomiting of significant grade.

On the 20th day of the second round of chemotherapy with 5-FU and cisplatin, she experienced dizziness with nystagmus, but these symptoms resolved with conservative management. Fifteen days after the dizziness episode, she showed acute onset disorientation, headache, and lethargy. Her mental status showed confusion, but neither focal neurological signs nor pathological reflexes were noted. Her blood pres-
sure was 110/70 mmHg, pulse rate 110/min, respiratory rate 14/min, and body temperature 36.4°C. Her myelosuppres-
sion status after chemotherapy was a white blood cell count of 1,300/μL (neutrophils 74.4%, lymphocytes 14.3%), hemoglobin concentration of 8.1 g/dL, and platelet count of 62,000/
μL. At that time, the level of serum BUN and creatinine were 10 mg/dL and 0.6 mg/dL. Her serum sodium and potassium were 133 and 3.5 mM/L, respectively. The total protein was 5.8 g/dL (reference range, 6.5-8.4 g/dL), serum albumin 3.6 g/dL (reference range, 3.5-5.1 g/dL), triglyceride 67 mg/
dL (reference range, 28-150 mg/dL), cholesterol 68 mg/dL (reference range, 130-240 mg/dL), and magnesium 1.9 mg/dL (reference range, 1.9-3.1 mg/dL). The body weight of the pa-
tient at diagnosis was 52 kg and was 54 kg at the time of this event. Her serum folic acid concentration was 2 ng/mL (ref-
erence range, 3-17 ng/mL), vitamin B12 concentration 1,259 pg/mL (reference range, 253-1,090 pg/mL), and thiamine concentration 138.1 ng/dL (reference range, 21.3-81.9 ng/dL). The ammonia concentration was normal. Brain magnetic res-
one imaging (MRI) showed symmetrical high signal intens-
ities in the posterior aspect of the medulla and periaqueduct-
ual area of the midbrain that were consistent with Wernicke’s encephalopathy. A small amount of subdural hematoma in
the right posterior occipital area was noted (Fig. 1A). She was
given intravenous thiamine, 500 mg for 5 days, and then oral
thiamine, 60 mg/day, even though the initial serum thiamine
level was normal. Her confused mental state resolved after
several hours, and her dizziness and nystagmus gradually im-
proved over the next 5 days.

The brain MRI was repeated in the outpatient clinic 1 mon-
th after the episode. The MRI showed nearly complete res-
olution of the previous abnormal signal intensities in the pos-
terior aspect of the medulla and the periaqueductual area of
the midbrain, including the subdural hematoma (Fig. 1B).

**DISCUSSION**

Neurotoxicity is an uncommon side effect of 5-FU ther-
apy. There are two types of toxicity, classified according to the
time of onset of symptoms. Acute toxicity manifests as a dif-
fuse encephalopathy or a cerebellar syndrome, is dose-relat-
ed, and is generally self-limiting. Delayed toxicity appears
several months later, is characterized as subacute multifocal
leukoencephalopathy, is immune-mediated, and responds to
corticosteroid treatment (3, 4). About 5% (range, 0.6-7%)
of patients treated with 5-FU experience neurotoxicity (3).
In a study by Yeh and Cheng, 5.57% of patients developed
5-FU-related encephalopathy (5).

Wernicke’s encephalopathy is characterized by an acute
onset of symptoms that may include changes in mental sta-
tus, ocular abnormalities and motor problems such as unco-
ordinated gait and ataxia, but this triad of symptoms is seen
in only 16% of patients (6). Wernicke’s encephalopathy can
be caused by thiamine deficiency associated with chronic alco-
hol abuse, malnutrition or unbalanced nutrition, gastrointesti-
nal surgery, recurrent vomiting, chronic diarrhea, systemic
illness, or magnesium depletion, all of which can affect thi-
amine uptake and utilization (7-9). Wernicke’s encephalopa-
thy can be diagnosed primarily from the clinical features, and
it should be confirmed by symptomatic improvement with
thiamine treatment (10). MRI is currently considered the
most valuable method to confirm a diagnosis of Wernicke’s encephalopathy. MRI has a sensitivity of 53% and a high sp-
ecificity of 93%, so it can be used to rule out other disorders.
In Wernicke’s encephalopathy, MRI studies typically show
an increased T2 signal that is bilaterally symmetrical in the
paraventricular regions of the thalamus, the hypothalamus,
mammillary bodies, the periaqueductal region, the floor of
the fourth ventricle, and the midline cerebellum (6).

---

**Fig. 1.** (A) The initial MRI demonstrates symmetric high signal intensities in the posterior aspect of the medulla and the periaqueductual area of the midbrain (narrow arrows) and an occipitoparietal hem-
atoma (broad arrows). Axial FLAIR. (B) Follow-up MRI 1 month later shows nearly complete resolution of the previous abnor-
mal signal intensities in the posterior as-
pect of the medulla, the periaqueductual
area of the midbrain, and the occipitopari-
etal hematoma.
A Case of Wernicke's Encephalopathy Following Fluorouracil-based Chemotherapy

Wernicke's encephalopathy following chemotherapy with 5-FU has been reported rarely (11). Although the biochemical basis for the neurological toxicity of 5-FU is not fully understood, it may be related to blockade of the Krebs cycle by fluorooacetate, a product of fluorouracil catabolism; another possibility relates to thiamine deficiency. Either possibility means that 5-FU-induced CNS neurotoxicity can manifest as Wernicke's encephalopathy. Thiamine phosphate is the active form of the vitamin, but its formation from thiamine can be blocked by 5-FU, an action that could further exacerbate preexisting thiamine deficiency in cancer patients (3).

Askoy et al. prospectively followed 35 patients receiving 5-FU-based chemotherapy and treated thiamine-deficient patients with vitamin supplements (12).

Historically, most 5-FU-associated neuropathies developed during 5-FU infusion or shortly after 5-FU completion. Our patient developed Wernicke's encephalopathy after 5 weeks of initial 5-FU exposure, but at that time, the concentration of thiamine was not low, although this measurement is limited by a lack of specificity and technical difficulties (6). The nutritional status of our patient was improving after several weeks, although her nutritional intake remained lower than normal because of mouth dryness induced by the previous concurrent chemoradiation of the head and neck cancer. It appears that the 5-FU could have caused the Wernicke's encephalopathy in our patient despite the small dietary deficiency, because she was not in severe malnutritional status judging from the total protein, albumin, triglyceride, and magnesium levels and her relatively improving appetite. A deficiency in dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme responsible for the catabolism of 5-FU, may be associated with this type of neurotoxicity, gastrointestinal toxicity, and myelosuppression (4). We did not measure the DPD level in this patient, but the concurrent myelosuppression might reflect her low DPD level indirectly. In addition, cisplatin combined with 5-FU can induce neurotoxicity, but this complication manifests mainly as a peripheral sensory neuropathy, although it may occasionally induce encephalopathy with or without seizure (13), and it has not been reported in relation to thiamine. Our patient was given a higher dose of cisplatin in a previous concurrent chemoradiation stage, but this did not produce any neurological abnormality.

We postulate that this patient had barely escaped the marginal thiamine deficiency during cancer and therapy, and the subsequent exposure to 5-FU aggravated the dietary imbalance and caused the encephalopathy. The clinical neurological symptoms and radiological abnormalities were reversed with adequate replacement of thiamine, which differs somewhat from traditional Wernicke's encephalopathy. Some therapies for malignancy have induced Wernicke's encephalopathy caused by a lack of thiamine supplementation with total parenteral nutrition, fast-growing neoplastic cells, vomiting and poor appetite. Moreover the use of specific chemo-

therapy agents such as 5-FU and ifosfamide can induce this neurological disorder (6, 14). Thus, it is important to confirm the clinical suspicion of Wernicke's encephalopathy associated with thiamine deficiency in treating cancer patients.

In conclusion, physicians should be aware of neurological signs in cancer patients treated with 5-FU, regardless of the CNS involvement of the tumor, especially if the patient is at risk of dietary deficiency.

REFERENCES

1. Kummar S, Noronha V, Chu E. Antimetabolites. In: DeVita VT, Hellman S, Rosenberg SA, eds. Cancer: principles and practice of oncology. 7th ed. volume 1. Philadelphia: Lippincott Williams & Wilkins 2005: 361-4.
2. Sausville EA, Longo DL. Principles of cancer treatment: surgery, chemotherapy and biologic therapy. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, eds. Harrison's principles of internal medicine. 16th ed. volume 1. New York: McGraw-Hill: 2005: 476.
3. Pirzada NA, Ali II, Dafer RM. Fluorouracil-induced neurotoxicity. Ann Pharmacother 2000; 34: 35-8.
4. Kim YA, Chung HC, Choi HJ, Rha SY, Seong JS, Jeung HC. Intermediate dose 5-fluorouracil-induced encephalopathy. Jpn J Clin Oncol 2006; 36: 55-9.
5. Yeh KH, Cheng AL. High-dose 5-fluorouracil infusion therapy is associated with hyperammonaemia, lactic acidosis and encephalopathy. Br J Cancer 1997; 75: 464-5.
6. Sechi G, Sera A. Wernicke’s encephalopathy: new clinical settings and recent advances in diagnosis and management. Lancet Neurol 2007; 6: 442-55.
7. Attard O, Dietemann JL, Diemunsch P, Pottecher T, Meyer A, Calon BL. Wernicke encephalopathy: a complication of parenteral nutrition diagnosed by magnetic resonance imaging. Anesthesiology 2006; 105: 847-8.
8. Merkin-Zaborsky H, Ifergane G, Frisher S, Valdman S, Herishanu Y, Wirguin I. Thiamine-responsive acute neurological disorders in nonalcoholic patients. Eur Neurol 2001; 45: 34-7.
9. Chiossi G, Nei I, Cavazzuti M, Basso G, Facchinetti F. Hyperemesis gravidarum complicated by Wernicke encephalopathy: background, case report, and review of the literature. Obstet Gynecol Surv 2006; 61: 255-68.
10. Seo IS, Lee SH, Kim SH, Kim WS, Lee KS, Song SK, Lee WG, Kim EH, Choi YW, Lee YU. A case of acute coma & respiratory arrest in Wernicke’s encephalopathy caused by malnutrition. Korean J Med 1998; 55: 137-44.
11. Kondo K, Fujiwara M, Murase M, Kodera Y, Akiyama S, Ito K, Takagi H. Severe acute metabolic acidosis and Wernicke’s encephalopathy following chemotherapy with 5-fluorouracil and cisplatin: case report and review of the literature. Jpn J Clin Oncol 1996; 26: 234-6.
12. Aksoy M, Basu TK, Brient J, Dickerson JW. Thiamin status of patients treated with drug combinations containing 5-fluorouracil. Eur J Cancer 1980; 16: 1041-5.
13. Steeghs N, de Jongh FE, Sillevis Smitt PA, van den Bent MJ. Cisplatin-induced encephalopathy and seizures. Anticancer Drugs 2003; 14: 443-6.

14. Hong SH, Kim ES, Roh YW, Jung SK, Chung C, Kong HS, Yun CB, Kang SS, Lee SK, Hwang HY, Bang SM, Cho EK, Shin DB, Lee JH. A case of iatrogenic Wernicke’s encephalopathy following chemotherapy and total parenteral nutrition. Korean J Hematol 2001; 36: 95-9.