Wernicke-Korsakoff Syndrome in Primary Peritoneal Cancer

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Key Words
Wernicke encephalopathy · Primary peritoneal cancer · Thiamine

Abstract
Wernicke encephalopathy is a disease that constitutes a medical emergency, but one that can be reversed with thiamine repletion if it is recognized early. Patients with cancer have a high risk of Wernicke encephalopathy because of malnutrition, the use of chemotherapeutic agents, and disease progression. Korsakoff syndrome can follow or accompany Wernicke encephalopathy. Although patients can recover from Wernicke encephalopathy via rapid repletion of thiamine, few patients recover from Korsakoff syndrome. Here, the case of a 76-year-old female patient who had primary peritoneal cancer and developed Wernicke-Korsakoff syndrome as a result of prolonged nutritional imbalance and fast-growing tumor cells is reported. The patient’s neurologic symptoms improved, but she did not recover from the psychiatric effects of the disease.

Background
Wernicke encephalopathy is a neuropsychiatric syndrome associated with thiamine deficiency. The incidence of Wernicke encephalopathy in adults is 0.8–2.8% per year at risk [1]. Wernicke encephalopathy is difficult to diagnose because its clinical symptoms are nonspecific. However, delays in treatment can result in coma and death. Patients with cancer have several risk factors for Wernicke encephalopathy, including the use of chemotherapeutic agents, nutritional imbalance, performance of bypass surgery, and disease progression due to fast-growing tumor cells. The classical symptoms of Wernicke encephalopathy are global confusion, ataxia, and ophthalmoplegia, but only one third of patients present with all of these classical symptoms [1]. Korsakoff syndrome, which is characterized by a chronic,
striking loss of working memory, often follows or accompanies Wernicke encephalopathy [1]. Although Wernicke encephalopathy can be resolved by rapid repletion of thiamine, Korsakoff syndrome cannot be resolved. This is the first reported case of Wernicke-Korsakoff syndrome in a patient with primary peritoneal cancer.

**Case Presentation**

A 76-year-old woman with primary peritoneal cancer and multiple lymph node metastases received 6 cycles of paclitaxel and carboplatin. After the 6 cycles of chemotherapy, partial response was achieved. Six months after her last chemotherapy cycle, she was admitted to the hospital because of sustained nausea and general weakness, which she had experienced for several months. Chest and abdominal-pelvic computed tomography scans showed that peritoneal metastasis and lymph node metastasis had progressed. Her serum CA-125 level was elevated (1,655 U/ml). She received continuous parenteral nutrition because of intractable nausea. Four days after admission, she developed disorientation and dizziness, which were followed by ataxia and diplopia. A neurologic examination indicated that she had ophthalmoplegia. Her laboratory findings were as follows: white blood cell count 6.59 × 10⁹/l, hemoglobin 12.0 g/dl, hematocrit 35.8%, blood platelet count 230 × 10⁹/l, serum total protein 6.1 g/dl, albumin 3.3 g/dl, glucose 111 mg/dl, aspartate aminotransferase 21 IU, alanine aminotransferase 14 IU, blood urea nitrogen 9.0 mg/dl, creatinine 0.15 mg/dl, Na 139 mM, K 4.6 mM, Cl 107 mM, and Ca²⁺ 0.98 mg/dl. There was no evidence of systemic infection or brain metastasis. Magnetic resonance imaging (MRI) of the brain showed hyperintensity in the mammillary body, medial aspects of both halves of the thalamus, cerebral aqueduct, tectal plate, and dorsal medulla on T2 fluid-attenuated inversion recovery (FLAIR) images (fig. 1). The patient’s serum thiamine level was 2.0 μg/dl (normal range 2.0–7.2 μg/dl). These findings were consistent with Wernicke encephalopathy. Thiamine (100 mg) was urgently administered intravenously, and ataxia and diplopia improved 2 days after thiamine injection. The other symptoms improved gradually. Fifteen days after the thiamine injection, she had recovered from her symptoms but displayed anterograde amnesia and disorientation with respect to time. A follow-up MRI scan of the brain showed improvement in the abnormal lesion (fig. 2).

**Discussion**

Wernicke encephalopathy is a neuropsychiatric syndrome that involves thiamine deficiency. The classic clinical triad of Wernicke encephalopathy comprises nystagmus and ophthalmoplegia, changes in mental status, and ataxia [2]. Predisposing factors for Wernicke encephalopathy include a staple diet of polished rice, chronic alcohol abuse, chronic malnutrition, gastrointestinal surgical procedures, recurrent vomiting, chronic diarrhea, cancer, use of chemotherapeutic agents, systemic disease, magnesium depletion, the use of chemical compounds (including drugs), and unbalanced nutrition [2].

Thiamine is an important coenzyme in intermediated carbohydrate metabolism, lipid metabolism, the production of amino acids, and the production of glucose-derived neurotransmitters [2]. These metabolic processes are essential biochemical pathways in the brain and peripheral nervous system. Thiamine deficiency mainly results in changes to the macroscopic and microscopic findings of brain lesions. Notably, 100% of patients with Wernicke encephalopathy show typical histopathological changes in the medial dorsal...
thalamic nucleus [2]. Additionally, one third of patients show histopathological changes in the superior vermis of the cerebellum [2].

The clinical features of Wernicke encephalopathy are nonspecific. Several reports have shown that some cases of thiamine deficiency are related to cancer [3–7]. Causes of thiamine deficiency in cancer patients include the use of thiamine by fast-growing neoplastic cells, poor dietary intake (which is related to appetite and nausea), significant malabsorption, and the use of specific types of chemotherapeutic agents [2]. In the present case, thiamine deficiency was probably related to fast-growing neoplastic cells and poor dietary intake. The patient recovered completely from ophthalmoplegia after a few hours, from ataxia after a few days, and from mental changes after 2–3 weeks of thiamine replacement therapy [2]. However, irreversible brain damage or death occurs in approximately 20% of cases of Wernicke encephalopathy, and the chronic irreversible form of the encephalopathy (Korsakoff syndrome) is associated with a survival rate of approximately 85% [2]. In the present case, the patient recovered from ophthalmoplegia, ataxia, and mental changes. However, she developed new symptoms of anterograde amnesia and disorientation with respect to time.

Many reports have described cases of Wernicke encephalopathy in patients with cancer, but Korsakoff syndrome has not been reported in such patients. Indeed, this is the first reported case of Wernicke-Korsakoff syndrome in a patient with primary peritoneal cancer. In addition, it is difficult to diagnose Wernicke encephalopathy if the patient has developed neurologic symptoms related to his or her cancer, because neurologic symptoms in patients with cancer can be related to many factors, such as electrolyte imbalance, cerebral metastasis, chemotherapeutic treatments, infection, and opioid overdose [6].

To diagnose Wernicke encephalopathy, it must first be suspected clinically. Wernicke encephalopathy is confirmed by measuring blood thiamine concentration or red blood cell transketolase activity. In our case, the blood thiamine level was 2.0 μg/dl, which is the lower limit of normal. However, this is not a definitive diagnostic test, given its limited specificity. An isocratic high-performance liquid chromatography method for thiamine, thiamine phosphate, and thiamine diphosphate in human erythrocytes is suitable for diagnosing Wernicke encephalopathy, but this test was not available. MRI is a valuable tool for confirming a diagnosis of Wernicke encephalopathy; it has a high specificity of 93% and a sensitivity of 53% [2]. In the present case, MRI findings were characteristic of Wernicke encephalopathy. A follow-up MRI scan showed improvement in the previously abnormal findings, but Korsakoff syndrome remained.

Primary peritoneal cancer is a rare cancer with a behavior that is very similar to epithelial ovarian cancer. The development of Wernicke encephalopathy has been reported in patients with gastrointestinal tract cancer, head and neck cancer, lung cancer, breast cancer, lymphoma, and leukemia; however, Wernicke-Korsakoff syndrome has not been reported previously in patients with primary cancers [3–5, 7–9]. The case reported here involved Wernicke-Korsakoff syndrome in a patient with primary peritoneal cancer. The patient rapidly recovered from neurologic symptoms and signs, but Korsakoff syndrome persisted. Therefore, clinicians should consider Wernicke encephalopathy in cancer patients with risk factors for this disease, such as nutritional imbalance due to long-term parenteral nutritional supply, use of chemotherapeutic agents, and fast-growing tumor cells. Clinicians should remember that Wernicke encephalopathy occurs in patients with unbalanced nutrition, as well as in those with subacute or chronic disease that increases metabolism.
References


Fig. 1. T2 FLAIR imaging of Wernicke encephalopathy. a Hyperintensity in the hypothalamus. b Hyperintensity in the medial aspects of both halves of the thalamus.
Fig. 2. T2 FLAIR imaging after recovery of Wernicke encephalopathy. a Disappearance of hyperintensity in the hypothalamus. b Disappearance of hyperintensity in the medial aspects of both halves of the thalamus.