
Severe Acute Metabolic Acidosis and Wernicke's Encephalopathy Following Chemotherapy with 5-Fluorouracil and Cisplatin: Case Report and Review of the Literature

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A 28-year-old woman with inoperable gastric carcinoma was given continuous infusion of 5-fluorouracil (5-FU) and low-dose cisplatin (CDDP) for 4 weeks while receiving intravenous hyperalimentation (IVH). Eleven days after her last treatment, she developed acute diplopia, deafness and gait ataxia, followed by severe confusion. She became markedly acidotic and hypotensive with a systolic blood pressure of 60 mmHg, necessitating intubation, dopamine treatment and hemodialysis for 7 h. She was also given thiamine. Thereafter, her blood pressure stabilized, the acidosis improved, and her deafness, diplopia, and confusion were resolved. This case suggests that FP (5-FU/CDDP) therapy toxicity, manifested as acute metabolic acidosis and Wernicke's encephalopathy, may be associated with IVH and thiamine deficiency.

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Key words: Thiamine deficiency—5-Fluorouracil—Cisplatin—Wernicke's encephalopathy

Introduction

5-Fluorouracil (5-FU) is the most effective chemotherapeutic agent for gastric cancer. A recent prospective randomized trial conducted as part of the Mid-Atlantic Oncology Program (MAOP) has shown that continuous infusion of 5-FU is superior to a bolus schedule in terms of both response rate and toxicity.¹⁾ Cisplatin (CDDP), an agent with superior anti-neoplastic activity against a variety of human tumors, has also been shown to potentiate 5-FU cytotoxicity.²⁾ FP (5FU/CDDP) therapy, in particular, is commonly used because it has less toxicity while providing a relatively high response rate.³⁾

The commonly reported side effects of 5-FU chemotherapy include nausea, diarrhea, and stomatitis. Alopecia and other dermatologic toxic effects (hyperpigmentation) and cardiotoxicity⁴⁾ have also been reported. Ototoxicity⁵⁾ has been reported as a side effect of cisplatin, along with bone marrow suppression, nephrotoxicity and gastrointestinal dis-

orders.

We report a patient who developed acute neurotoxicity and acidosis after systemic chemotherapy with continuous infusion 5-FU and consecutive low-dose cisplatin. The possible mechanisms are discussed and the literature related to this rare complication is reviewed.

Case Report

A 28-year-old woman was referred to our hospital for evaluation of a 2-month history of dysphagia. Laboratory data on admission included a red blood cell count of $4.08 \times 10^6/\text{mm}^3$, a hemoglobin level of 12.3 g/dl, a white blood cell count of $4000/\text{mm}^3$, and a platelet count of $14.5 \times 10^4/\text{mm}^3$. Her electrolyte concentrations were within normal limits. A serum liver chemistry profile showed GOT 11 IU/l, GPT 6 IU/l, TTT 13 U, and ZTT 14.4 U. The level of total protein was low at 5.5 mg/ml. An upper gastrointestinal series demonstrated a diffusely infiltrating carcinoma invading from the angle to the fornix. Histologic examination of endoscopic biopsy specimens demonstrated a poorly differentiated adenocarcinoma. Computed tomography (CT) of the abdomen showed gastric carcinoma with multiple lymph node metastases and ascites. The patient was judged ineligible for cura-

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tive gastrectomy and was treated with a regimen of 24-h continuous infusion 5-FU (330 mg/m²/day) plus bolus infusion of low-dose CDDP (6 mg/m² daily) d1–5. This regimen was repeated every 4 weeks with intravenous hyperalimentation (IVH) without vitamin supplementation.

Before the chemotherapy, the patient was unable to eat because of cancer-induced stenosis of the esophagus. Three weeks after the first cycle, her dysphagia improved slightly, but her oral intake was poor. She developed WHO grade 2 leukopenia but recovered after 3 days of steroid injections. Four weeks after the first cycle, she showed no objective response (NC). On the sixth day after the end of chemotherapy, the patient complained of dizziness and autophony. An audiogram showed a normal range of hearing but nystagmus was evident. On the 11th day, she developed acute diplopia, deafness, gait ataxia, and then severe confusion. She was found to be markedly acidotic (pH 7.316) with a base excess of -13.6, and hypotensive with a systolic blood pressure of 60 mmHg, necessitating intubation, treatment with dopamine, and hemodialysis for 7 h. She was also given thiamine. Subsequently, her blood pressure stabilized, the acidosis improved and the deafness, diplopia, and confusion were resolved. Four weeks after the first cycle, the serum 5-FU level was 0.1 µg/ml. The total serum CDDP level tended to increase as the treatment progressed. The maximum concentration was 0.84 µg/ml. The blood concentration of free CDDP reached a peak of 0.38 µg/ml about 5 min after the end of administration, and became undetectable after about 1 h.

Discussion

The first report of 5-FU-induced neurotoxicity by Riehl and Brown⁶ described a syndrome of acute cerebellar dysfunction: non-coordination, nystagmus, slurred speech, and gait ataxia, which was considered to be a cerebellar syndrome characterized by acute onset and reversibility upon drug discontinuation. A subsequent study by Koenig and Patel⁷ suggested that 5-FU neurotoxicity was due to blockade of Krebs' cycle by fluorocitrate, although the mechanism of 5-FU toxicity remains undefined.

Aksoy *et al.*⁸ prospectively studied 35 patients receiving 5-FU-based chemotherapy; thiamine deficiency developed during treatment, and the symptoms were reversed by thiamine supplementation. Recently, some case reports^{9, 10} have indicated a possible role of thiamine supplementation in the prevention of 5-FU neurotoxicity. The two major toxicities of thiamine deficiency involve the cardiovascular (wet beriberi) and nervous (dry beriberi) systems. In the acute type of wet beriberi, lactic

acidosis with abdominal pain, tachycardia, and tachypnea are the central features. Wernicke's encephalopathy as an acute form of dry beriberi can produce neurologic disorders characterized by disturbance of consciousness, ophthalmoplegia, nystagmus, and ataxia. These symptom complexes were quite similar to the neurological findings in the present case.

5-FU chemotherapy can further exacerbate existing thiamine deficiency.¹¹ Thiamine pyrophosphate (TPP) is the active form of the vitamin; experimental studies have shown that 5-FU exposure can increase the level of TPP. These results indicate that 5-FU may increase cellular thiamine metabolism, possibly resulting in thiamine deficiency.¹²

We have described a rare case of FP therapy toxicity, manifested as severe acute metabolic acidosis and Wernicke's encephalopathy, associated with IVH. The serum levels of 5-FU and CDDP were within the normal range during the FP therapy. The patient's symptoms developed after the chemotherapy treatment, and were resolved by hemodialysis and thiamine supplementation. Unfortunately, pretreatment thiamine levels were not obtained, although the response to thiamine supplementation suggests that thiamine deficiency induced the symptoms. Furthermore, in the present case, IVH may have exacerbated the existing thiamine deficiency. The first report of IVH-induced Wernicke's encephalopathy by Blenow¹³ described mental confusion, nystagmus, and gait ataxia, which were managed by thiamine administration. Severe lactic acidosis has been reported during IVH without vitamin supplementation.¹⁴ Thiamine is an essential cofactor needed for the conversion of pyruvate to acetylcoenzyme A and entry to Krebs' cycle. Thus, the requirement for thiamine increases during IVH.

We previously reported 31 patients treated with a combination of 5-FU and low-dose CDDP (FLDP).¹⁵ Toxicity was primarily hematologic: leukopenia and thrombocytopenia of World Health Organization (WHO) grade 3 or 4 occurred in 4/31 (13%) and 4/31 (13%) of patients, respectively, which was low in comparison with other forms of FP therapy. However, one patient developed the rare toxicity reported here.

Nutritional deficiencies are common among cancer patients and IVH is often used for nutritional support in patients undergoing chemotherapy for advanced carcinoma. FP therapy is becoming more widely used for patients with gastric cancer. Although acute metabolic acidosis and Wernicke's encephalopathy is rare and avoidable, it may occur more often with IVH.

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