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A Case of Neurotoxicity Following 5-Fluorouracil-based Chemotherapy

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5-Fluorouracil (5-FU) is a commonly used chemotherapeutic agent. However, its neurotoxicity is rare and not well recognized. We report a case of 5-FU neurotoxicity with organic brain syndrome and progression to multifocal leukoencephalopathy in a 44-year-old male patient having malignant gastrointestinal stromal tumor. 5-FU-induced neurotoxicity should, therefore, be considered as an important differential diagnosis in cancer patients with neurological abnormality and history of chemotherapy.

Key Words : *Fluorouracil; Neuorotoxicity syndromes; Leukoencephalopathy, progressive multifocal*

INTRODUCTION

5-Fluoruracil (5-FU), pyrimidine antimetabolite, is a chemotherapeutic agent widely used for various tumors[1]. Common side effects of 5-FU include mucositis and myelosuppression. Neurotoxicites of 5-FU with manifestations of somnolence, upper motor neuronal signs, cerebellar ataxia and a cluster of symptoms and signs of organic brain syndrome[1] have rarely been reported. We report a case of serious neurotoxicity following 5-FU infusion for malignant gastrointestinal stromal tumor (GIST) and also briefly review 5-FU related neurotoxicity.

CASE

A 44-year-old male patient received his first cycle of palliative 5-day chemotherapy containing 5-FU (800 mg/m^2), adriamycin (40 mg/m^2) and mitomycin- C (8 mg/m^2) for a recurrent, massive, malignant gastrointestinal stromal tumor (GIST) which developed at 3 years after surgery. His tumor was about 20 cm in diameter and invaded the urinary bladder and sigmoid colon (Figure 1). About 1 week after the completion of his first cycle of chemotherapy, he displayed slurred speech and inappropriate behavior for 3~5 days at home. Such abnormal symptoms improved

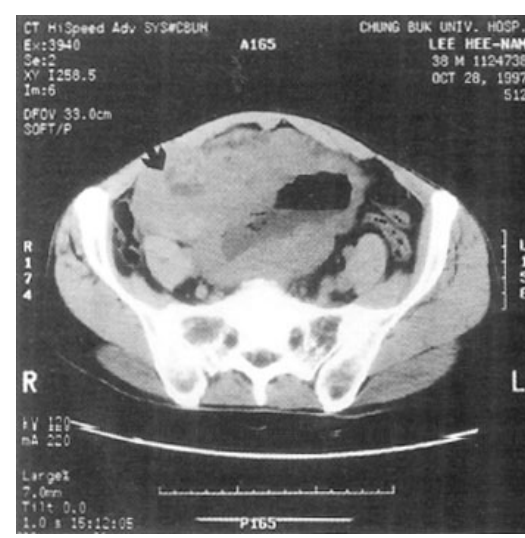

Figure 1. Abdominal CT shows a large tumor at pelvic cavity

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spontaneously. On the beginning of the second cycle of chemotherapy, he appeared well and no remarkable abnormality was found on physical examination and laboratory test. His mental status was normal. He received the second cycle of chemotherapy with the same regimen as the first and was discharged without any complaint. On the 7th day after the completion of his second chemotherapy, his mental status deteriorated with slurred speech, inappropriate language, hyperventilation, insomnia, disorientation and incontinence of stool and urine. He was admitted to our hospital via the emergency room (ER). At the ER, his vital signs were as follows: blood pressure 120/70 mmHg, pulse rate 92/minute, respiration rate 24 /minute and body temperature 36.8℃. On physical examination, there was no noticeable abnormality except abnormal mental status with poor communication. Neurological examination revealed confused mental status, bizarre behavior, lethargy, slurred speech and somnolence. Light reflex was prompt with symmetric, isocoric pupils. Orientation to time, person and place was lost. However, he showed neither focal neurological sign nor pathological reflex. On the laboratory findings, white blood cell count was 3,020/uL, hemoglobin 11.0 g/dL and platelet count 107,000/uL. BUN and creatinine were 24.0 mg/dL and 1.4 mg/dL, respectively, serum natrium 135.0 mEq/L, serum pottasium 4.3 mEq/L, ionized calcium 4.25 mg/dL and serum albumin 2.9 g/dL. On arterial blood gas analysis (ABGA), respiratory alkalosis pattern was found with pH 7.546, pCO_2 19.3 mmHg, pO_2 133.3 mmHg, bicarbonate 16.8 mEq/L and O_2 saturation 99.4 % at room air. His serum ammonia level was at 326 ug/dL, higher than the upper limit of normal range (0~150 ug/dL). Chest x-ray was normal, abdominal simple x-ray showed mild paralytic ileus pattern. Brain computed tomography at the ER was normal without evidence of metastasis or cerebral vascular accident. After a few sessions of lactulose enema, his mental status recovered somewhat with intact orientation to persons. During the admission period for 15 days, his mental status and general condition gradually recovered. He complained of intermittent abdominal pain and gastric distension due to partial obstruction of the proximal small bowel by the mass. Cerebellar function tests, such as finger to nose, rapid alternative test, heel to shin test and Romberg test, were all negative. Motor and sensory function of the extremities were normal. Electroencephalography (EEG) showed moderate, diffuse cerebral dysfunction (Figure 2). Brain magnetic resonance imaging revealed no abnormal lesion in brain parenchyma. His mental status and general

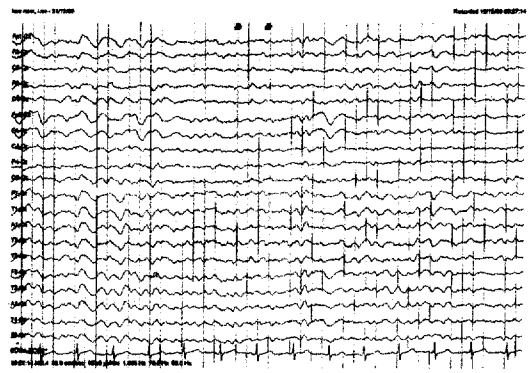

Figure 2. EEG findings show continuous, diffuse theta and delta with slowing of background activity and poorly regulated posterior dominant rhythm

condition recovered, so that we changed the chemotherapeutic regimen to adriamycin (60 mg/m^2) and cisplatin (60 mg/m^2) for 1 day, omitting 5-FU. He was discharged without any problem. On the 5th day of postchemotherapy, he was in stuporous mentality and lethargic condition. At ER, he was found to have neutropenic fever and sepsis syndrome with pancytopenia, respiratory alkalosis and hypokalemia. WBC was 160/uL and platelet count was 53,700/uL. Cerebrospinal fluid (CSF) study was normal in pressure, cell count and chemistry. On blood culture, *Staphylococcus aureus* was found. After treatment with intravenous fluids and broad-spectrum antibiotics, his mental status and general condition rapidly improved for 2~3 days. On the 17th day after the 3rd chemotherapy, he was discharged since he completely recovered from sepsis syndrome. After discharge, he intermittently experienced altered mentality which developed after constipation and abdominal distention. His neurological symptoms were relieved after repeated lactulose enema at a local hospital. On the last visit after 2 months of 5-FU administration, he still displayed slightly slurred speech and slowly progressive cachexia. Brain magnetic resonance imaging revealed newly developed hyperintense lesions in the bilateral cerebellar hemisphere, thalami and midbrain on T2WI without mass effect. On T1WI, hypertensive lesion was developed in bilateral basal ganglia (Figure 3). These findings were compatible with multifocal leukoencephalopathy.

There are many reports on serious neurotoxicity of 5-FU in patients with dihydropyrimidine dehydrogenase (DPD) deficiency. DPD is the rate-limiting enzyme of 5-FU catabolism and is encoded by the human dihydropyrimidine dehydrogenase gene (*DPYD*)[2]. So far, about 20 different

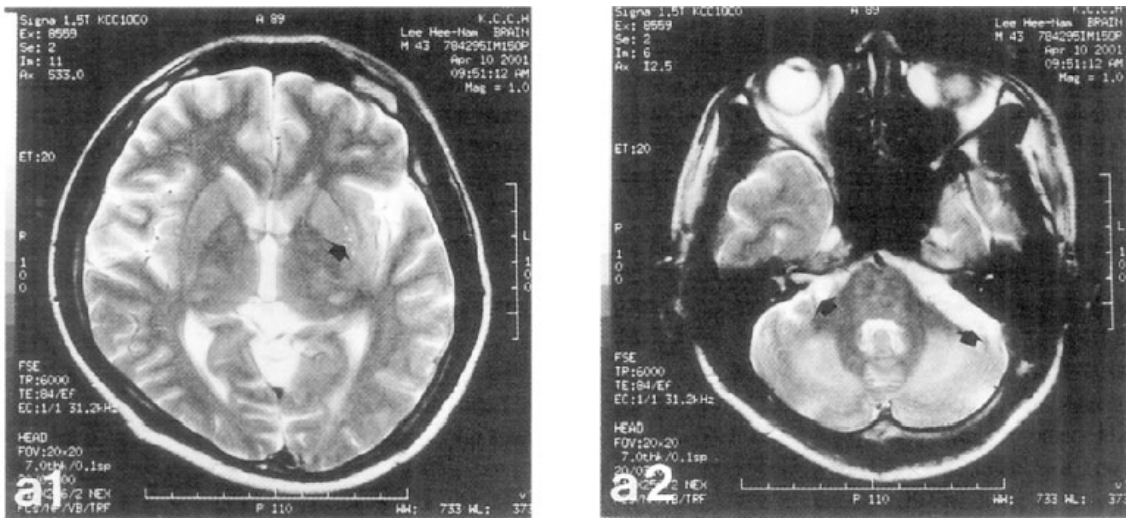

Figure 3. Brain magnetic resonance imaging (unenhancing) shows hyperintensive lesions in bilateral cerebellar hemispheres (a1, arrow), thalami and midbrain (a2, arrow) on T2WI without mass effect

mutations of *DPYD* have been reported in DPD deficient subjects[16]. G to A point mutation within the 5'-splicing site (GT to AT), also known as DPYD×2a (intron 14 G1A), is one of the common mechanisms for DPD deficiency[17]. Therefore we examined the presence of DPYD×2a (intron 14 G1A) by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). When a PCR-RFLP based genotyping was performed[1], fragments of 278 and 131 bp were produced by the restriction endonuclease Mae II in the wild type allele. However, the mutant allele had no restriction site and remained undigested (409 bp). Therefore, as shown in Figure 4, this patient had a wild-type pattern.

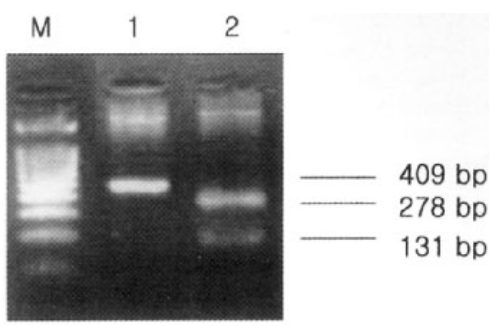

Figure 4. PCR genotyping assay to detect GT to AT mutation. Wide-type DPYP allele gives fragments of 278 and 131 bp bands, whereas the mutant allele gives a unique 409 bp band after Mae II restricition. Lanes 1 and 2 correspond to homozygote mutant and wild-type (patient), respectively. M is 1-kb DNA ladder size markers.

DISCUSSION

Although both acute and delayed forms have been reported, fluorouracil-induced neurotoxicity is rare. The acute form consists of cerebellar syndrome and encephalopathy, whereas the delayed variety takes the form of subacute multifocal leukoencephalopathy[1, 3]. About 5% (0.6~7%) of the patients who received 5-FU have been reported to experience neurotoxic symptoms[3, 4, 9]. The clinical manifestations of acute cerebellar syndrome, such as ataxia, slurred speech and nystagmus, were first described by Riehl and Brown in 1964[4-6]. Encephalopathy or organic brain syndrome following 5-FU treatment is a less commonly observed neurotoxicity with confusion, disorientation and other cognitive disorders[7, 8]. Subacute multifocal leukoencephalopathy with typical brain magnetic resonance imaging findings of multifocal, enhancing white matter lesions and biopsy findings of demyelination[9] has been reported as a 5-FU sequela.

We reported a case of delayed form of 5-FU neurotoxicity characterized by subacute multifocal leukoencephalopathy. Our case initially showed moderate diffuse cerebral dysfunction on Electroencephalography (Figure 2) without abnormality in brain magnetic resonance imaging. During the 2 months after the last administration of 5-FU, the neurological symptoms waxed and waned depending on the partial obstruction of the bowel and did not fully recover. Follow-up brain magnetic resonance imaging revealed multifocal leukoencephalopathy (Figure 3). His

neurological symptoms were aggravated by transient bowel obstruction with increased serum ammonia. Lactulose enema helped his mental status. He received not only 5-FU but also adriamycin and mitomycin. However, we could not find any relevant papers on the neurotoxicities of adriamycin and mitomycin. Therefore, we attributed the neurotoxicity of our case to 5-FU.

5-FU is a pyrimidine antimetabolite which has to be metabolically activated within the cells and incorporated into both DNA and RNA, which results in DNA strand breakage and abnormal processing and function of RNA[10].

The biological basis for 5-FU neurologic toxicity is not well understood. 5-FU itself seems to be relatively nontoxic to the nervous system in laboratory animals[13] when administered intrathecally. Koenig *et al.* proposed that fluorocitrate, the major catabolite of 5-FU, inhibited Krebs cycle and a blockade of Krebs cycle impaired the activity of the urea cycle[3, 11]. Subsequently, encephalopathy was accompanied by hyperammonemia and lactic acidosis[3, 11]. Okeda *et al.* reported that, in animal experiments, direct toxic effect on myelin with splitting of the intraperiodline and vacuole formation was not due to 5-FU itself, but to monofluoroacetic acid and α-fluoro-β-alanine (the major catabolites of 5-FU)[12]. The other explanations for 5-FU neurotoxicity, such as induction of thiamine deficiency and inherited deficiency of the enzyme dihydropyrimidine dehydrogenase (DPD)[4, 14], have also been presented.

The frequency of low and deficient DPD activity in the general population is estimated to be 3~5% and 0.1%, respectively[18]. Recent efforts to explain the relationship between genotype and phenotype in patients with DPD deficiency have brought much progress[16, 17]. DPD protein is encoded by *DPYD*, which is a large gene (> 950 kb) containing 23 exons with approximately 3 kb of coding region[19, 20]. To date, about 20 variant *DPYD* alleles, containing single amino acid substitutions, nucleotide deletions or a donor splice site mutation resulting in exon skipping, have been described[16]. Among them, G to A point mutation within the 5'-splicing site (intron 14 G1A) is the most common (2.2% out of 90 alleles in Finnish and 2.7% out of 72 alleles in Taiwanese general population) and analytical methods for this mutation are well established[1]. Although this mutant allele was not found in our case, a possibility of decreased DPD activity by other *DPYP* mutations could not be excluded.

As a chemotherapeutic agent, 5-FU is active against a wide variety of solid tumor, including cancers of gastrointestinal tract, ovary and breast[15]. The neurotoxicity of 5-FU has been very rarely reported. However, it is increasingly recognized. In cancer patients with neurological abnormality, there are many possible differential diagnoses, such as brain metastasis, infection of brain or meninges, sepsis syndrome, metabolic abnormality. Based on our present case, we emphasize that 5-FU-induced neurotoxicity should also be an important category of differential diagnosis in these patients. The treatment of 5-FU neurotoxicity is recommended as supportive care. In the literature, several treatments, such as thiamine infusion, glucocorticosteroid, uridine infusion, charcoal hemoperfusion or hemodialysis, were recommended. However, their efficiency has not been proven[10]. To understand the mechanism of neurological manifestation of 5-FU, further investigations are warranted.

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