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5-Flourouracil–Induced Encephalopathy in Parkinson's Disease

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ABSTRACT

A 59 year-old male with Parkinson's disease developed encephalopathy during adjuvant treatment of rectal cancer. Acute neurotoxicity related to high dose 5-Flourouracil infusion is well described, but encephalopathy with low dose bolus 5-Flourouracil is rare. The advanced Parkinson's disease patients may be more prone to hyperammonemia associated encephalopathy caused by 5-Flourouracil . The prompt recognition of the symptoms is key to diagnosis and treatment.

Keywords: Parkinson's disease, 5-Flourouracil, Rectum cancer, Encephalopathy

ÖZET

Parkinson Hastalığı Olan Bir Vakada 5-Florourasile Bağlı Gelişen Ensefalopati

Rektum kanseri nedeni ile adjuvant tedavi esnasında ensefalopati gelişen Parkinson hastalığı bulunan 59 yaşında bir erkek hastayı sunduk. Yüksek doz infüzyonel 5 florourasil infüzyonu ile ilişkili akut nörotoksisite iyi tanımlanmış olmasına rağmen düşük doz bolus 5 florourasile bağlı ensefelopati nadir rapor edilmiştir. İleri evre Parkinson hastalığı olan vakalar 5 florourasile bağlı oluşan hiperamonyemi ilişkili ensefalopatiye daha eğilimli olabilirler. Tanı ve tedavide semptomlarrın erken tanınması önemli rol oynamaktadır.

Anahtar Kelimeler: Parkinson Hastalığı,5-Florourasil, Rektum kanseri, Ensefalopati

INTRODUCTION

5-fluorouracil (5-FU) is a fluoropyrimidine analogue used in various combination regimens. Upon intravenous infusion, it diffuses into all compartments of the body including central nervous system. Calcium folinate augments entire effect of 5-FU including the diffusion into cerebral-spinal space. 5-FU is frequently used together with oxaliplatin in adjuvant treatment of colorectal cancer. Although tolerated relatively well; this combination frequently causes myelosupression, mucositis and diarrhea. The other common side effect is peripheral neuropathy and almost entirely caused by oxaliplatin. Here we report a patient who developed encephalopathy with low dose bolus 5-FU (500 mg/m^2 in 15 minutes) administration.

CASE REPORT

A 59 year old man was diagnosed with rectal adenocarcinoma in February 2009. His past medical history was significant for well controlled advanced Parkinson's disease for over 5 years which was treated with pramipexole hydrochloride hydrate 1 mg/day and Stalevo 3 tablets per day (Levodopa, karbidopa, entacapone, 100 mg, 25 mg, 200 mg respectively).

Initially he received neoadjuvant chemotherapy in the first four and last three days of radiation therapy (5-FU 425 mg/m^2 and Calcium folinate 20 mg /m^2) for radio sensitization. No significant toxicity was observed during that period. He underwent rectosigmoid resection in June 4, 2010. The pathology revealed a well differentiated adenocarcinoma and T2 tumor (involvement of submucosa and muscularis propria). None of the four sampled lymph nodes was involved with tumor. He then started on adjuvan Calcium folinate 200 mg/m^2 as a 2 hours IV infusion plus 5-FU 500 mg/m^2 IV bolus weekly for 6 weeks, and oxaliplatin 85 mg/m^2 as a 2 hour IV infusion on day 1, 15 and 29. Each cycle was repeated with 8 weeks intervals. During the third week of that treatment; 24 hours after the completion of the infusion, he developed nausea, vomiting and diarrhea. The next day he developed amnesia, incoherent speech and difficulty remembering appropriate words. The symptoms associated with Parkinson's disease in the past were not aggravated. The patient was admitted to neurological inpatient unit and underwent work-up including cranial MR which showed no evidence of metastasis or acute cerebrovascular event. EEG and chemical analysis of the cerebrospinal fluid also showed no abnormalities. He did not have renal, hepatic and nutritional abnormality. No evidence of paraneoplastic syndrome was evident and anti-neuronal antibodies Anti Hu(ANNA 1), Anti Ri(ANNA 2), Anti Tr(PCA-Tr) antibodies were not present. Lumbar puncture cytology and serological analysis did not show any abnormality including leptomeningeal seeding. Anti-neuronal antibody titer in cerebrospinal fluid was normal as well. Biochemical analysis of the serum including vitamin B_{12} and folic acid levels was unremarkable. He did not use any other medication throughout that time period.

Neurological examination showed confusion, disorientation in time, place and person and incoherent speech. Whole spectrum of symptoms significantly improved within 24 hours with supportive care only. The patient was given a two-week break for re-administration of chemotherapy. When the chemotherapy restarted oxaliplatin was omitted and 5-FU and Calcium folinate doses decreased by 25% to minimize the toxicity (5-FU 400 mg/m^2, Calcium folinate 150 mg/m^2). Two days after the administration of chemotherapy, he had similar neurological symptoms. Whole work up repeated again and it was unremarkable except serum ammonia level which was elevated to 140 μmol/L (normal range 16-60 μmol/L). The patient was admitted to the hospital and supportive care was initiated (including close monitoring of vital signs and administration of IV fluids, oxygen, antibiotics, and lactulose). Again the symptoms resolved within 24 hours. The adjuvant treatment terminated. His most recent follow up was in 14th of December and he was back to his baseline neurological status.

DISCUSSON

5-FU associated encephalopathy has been reported in the literature.[1] The incidence of encephalopathy with high dose infusional 5-FU can be as high as 5.7%.[2] In general, neurotoxicity frequency is between 0.9-7 percent.[3] It is described as an episode of confusional state[4] and this state is usually due to hyperammonemia, secondary to high dose 5-FU in-

fusion.[2] It is postulated that 5-FU metabolites inhibit Krebs cycle and due to that the urea cycle is disturbed which causes hyperammonemia.[5]

One other mechanism involved in 5-FU induced encephalopathy is dihydropyrimidine dehidrogenase deficiency.[6] This enzyme is responsible for the metabolism of 5-FU. When deficient, severe myelosupression and mucositis is observed, therefore our patient does not seem to have dihydropyrimidine dehidrogenase deficiency. It was not possible to determine dihydropyrimidine dehidrogenase activity or to analyse genetic polymorphisms of the enzyme in the present case.

The onset of 5-FU related encephalopathy is variable and is reported to be ranging from 0.5-5 days.[7] The spectrum of encephalopathy may include disorientation, neurosensory abnormalities, agitation, seizure stupor and coma. The symptoms generally resolve upon discontinuation of 5-FU infusion within 72 hours.[2] In our case both the time of onset and the resolution of the symptoms were within these reported ranges.

There is only one case of encephalopathy with low dose bolus 5-FU administration. That patient had 600 mg/m^2 bolus infusion of 5-FU which caused a similar picture.[8] Our patient's dose was even lower than that reported dose. The dopaminergic neurons of the midbrain are particularly sensitive to toxic cell death induced by hyperammonemia. It is also known that degeneration of midbrain dopaminergic neurons is characteristic of advanced idiopathic Parkinson's disease. Thus patients with advanced Parkinson's disease may be more vulnerable to hyperammonemia caused by 5-FU administration.[9]

CONCLUSION

In patients who receive 5-FU therapy, alteration in mental status should alert the physician for the possible diagnosis of 5-FU associated hyperammonemic encephalopathy. Once the diagnosis has been made chemotherapy should be discontinued immediately. Additional treatment is not necessary as the symptoms are generally completely reversible. Supportive care alone should be adequate. Complete recovery rate with cessation of therapy is reported as 93% in the literature.[2,9] The patients with advanced Parkinson's disease may be more vulnerable to hyperammonemia induced encephalopathy caused by 5FU administration and prompt recognition of the symptoms is key point for the diagnosis and treatment.

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