

5-fluorouracil-induced manic episode in patients with colon cancer. A case report and literature review

Gulcin Elboga¹, Perihan Gizem Aksoy¹, Tulay Kus², Elif Karayagmurlu¹, Gokmen Aktas³, Sengul Sahin¹, Abdurrahman Altindag¹

¹Gaziantep University Medicine Faculty Department of Psychiatry, Gaziantep, Turkey

²Adiyaman University, Training and Research Hospital, Clinics of Medical Oncology, Adiyaman, Turkey

³Kahramanmaraş Sutcu Imam University Faculty of Medicine, Department of Medical Oncology, Gaziantep, Turkey

Copyright © 2019 by authors and Annals of Medical Research Publishing Inc.

Abstract

The combination of 5-fluorouracil (5-FU), irinotecan and bevacizumab (FOLFIRI-beva) is one of the main treatment options for metastatic colon cancer. We present a rare case of irritable mood elevation during FOLFIRI-beva treatment in a man without psychiatric history. A 41-year-old man with colon cancer developed a manic episode after four cycles of chemotherapy. After excluding the other causes, the patient was diagnosed with Medication-induced Bipolar disorder manic episode with mixed features according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, fifth edition. Chemotherapy was discontinued, and antipsychotic treatment with haloperidol and biperidone was started. He recovered after 12 days. While adjustment disorders, depression and delirium are more common in cancer patients, mood disorders are rare during chemotherapy. Neuropsychiatric manifestations are uncommon during 5-FU treatment. Clinicians should keep in mind that a neuropsychological condition or mood disorders may be encountered during chemotherapy especially with 5-FU.

Keywords: 5-Fluorouracil; manic episode; mood disorder; colon cancer.

INTRODUCTION

A considerable number of cancer patients, approximately one-half, are experiencing psychiatric disorders before, during, or after the completion of treatment. Unfortunately, patients are struggling to cope with cancer itself, also treatment difficulties such as chemotherapy, radiotherapy, or surgery complications, decreased quality of life and as well as the psychological complications such as adjustment disorders, major depression, organic mental disorders, personality disorders, anxiety disorders, and delirium (1, 2). Decision making for the diagnosis and identifying patients who have a psychiatric disorders are difficult because psychiatric finding can be confused with treatment side effects, symptoms of the cancer or chemotherapy and disease-induced delirium. In this regard, clinicians should keep in mind that a disease or treatment induced psychiatric disorders during treatment process may be encountered especially for patients with advanced disease.

We present a rare case of manic episode during

5-fluorouracil–irinotecan–bevacizumab combination (FOLFIRI-beva) treatment in a man with no prior psychiatric history. While manic reactions have been reported following glucocorticoids, anabolic steroids and ifosfamide, rare cases have been reported during 5-FU-based treatment in the literature (3-8). We discussed these cases together with our patient to provide information to the literature.

CASE REPORT

A 41-year-old man was diagnosed with colon adenocarcinoma with synchronous metastases to distant colon segment. All macroscopically involved colon segments were removed. The patient did not have any other comorbidities, cardiovascular or neurologic disease and previous psychiatric diagnosis. There was no family history for psychiatric condition. Eastern Cooperative Oncology Group performance status of the patient was 0. The patient was a smoker but had no history of alcohol use or any substance abuse. After one month, a combination of leucovorin, 5-FU, irinotecan and bevacizumab

Received: 15.03.2019 **Accepted:** 05.04.2019 **Available online:** 17.04.2019

Corresponding Author: Gulcin Elboga, Gaziantep University Medicine Faculty Department of Psychiatry, Gaziantep, Turkey

E-mail: gulcincinpolat@yahoo.com

was administered. He received dexamethasone 8 mg intravenous (IV) before every cycle of chemotherapy for premedication. After four cycles of chemotherapy he developed persistently elevated, expansive or irritable mood psychomotor agitation, hyperactivity, insomnia. According to the information received from the relatives of the patient, there have recently been complaints of inappropriate behaviors, constant shouting and insulting to his relatives, aggression, decreased need for sleep, increased in goal-directed activity accompanied by loss of appetite, repetitive death thoughts, reduced speech and intimacy. The mood of the patient was labile. The patient experienced concurrent visual hallucinations. Among the best known of the medical conditions that can cause a bipolar manic or hypomanic condition are Cushing's disease and multiple sclerosis, as well as stroke and traumatic brain injuries. Other important differential diagnosis are substance use or medications that can induce manic symptoms (e.g., steroids). The most common etiological factors were ruled out through normal physical and neurological examination, urine test for any substance abuse, complete blood count, liver, renal, thyroid function test, brain imaging with computed tomography (CT) and electroencephalography (EEG). There was no history of narcotic analgesic use. After excluding the other causes, the patient was diagnosed with Medication-induced Bipolar disorder manic episode with mixed features according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, fifth edition. Chemotherapy was discontinued, and antipsychotic treatment with haloperidol 10 mg intramuscular twice a day and biperiden 5 mg intramuscular twice a day was started. After three days, medications were changed with orally form of haloperidol and biperiden as 10 mg and 2 mg three times a day, respectively. After 2 days chlorpromazine 100 mg tablet was added due to insomnia. His appetite and sleep cycles recovered after 12 days, and he followed one month with euthymic mood. Naranjo Adverse Drug Reaction Probability Scale score of this case is found 8. The relationship between adverse effect and drug is probable.

DISCUSSION

We report a patient with colon adenocarcinoma presenting with psychiatric manifestations probably related to administration of 5-Fluorouracil (5-FU). The neurologic toxicity of 5-FU is uncommon, though it usually presents with cerebellar, neuropsychiatric, focal neurological symptoms, and toxic encephalopathy 5-FU-induced neurologic toxicity may occur without other toxicities such as hematologic or gastrointestinal and is often reversible after discontinuation of treatment (9, 10). Neuropsychiatric symptoms including confusion, disorientation, and memory loss have been observed in approximately 5.7% of the patients (10,11). Previously, a case of 5-FU-induced acute psychosis presented with agitation, hallucination, and bipolar disorder during administration of combination of 5-FU, oxaliplatin and bevacizumab chemotherapy for colon carcinoma and

a case of woman with breast cancer who developed a manic episode while being treated with a 5-fluorouracil-epirubicin-cyclophosphamide combination were reported (5,6). We also reported a patient with 5-FU induced neurotoxicity predominantly manifested with psychotic symptoms as a manic disorder during FOLFIRI-beva treatment which is another combination regimen for the treatment of colon adenocarcinoma. Although the association between 5-FU and psychosis is not clearly established in this case, the development of psychosis during the chemotherapy administration, then resolving symptoms of manic disorder after discontinuation of chemotherapy with exclusion of the other possible factors supports the diagnosis of manic disorder.

Secondary mania may account for 1–2% of cases and there were a few cases describing the onset of mood symptoms after chemotherapeutic agents including ifosfamide, aromatase inhibitors, steroids and 5-FU (12, 13). Direct evidence of 5-FU induced neurotoxicity is lacking, however, increasing in ammonia, the end product of 5-FU, and fluoroacetate, the intermediate product of 5-FU, which directly inhibits the ATP-producing Krebs cycle may cause neurotoxicity with lactic acidosis and urea cycle defect (11). In our present case, 5-FU induced encephalopathy was excluded because of the absence of the typical findings such as diffuse cortical dysfunction with diffuse slow waves or diffuse intermittent theta waves in electroencephalogram (EEG) examinations. Also delirium, the most frequent neuropsychiatric complication in the oncological clinics characterized by the concurrent disturbances of level of consciousness, attention, thinking, perception, memory, psychomotor behavior, emotion, and the sleep-wake cycle, was excluded. Corticosteroids often induce psychiatric syndromes, including depression, mania, psychosis, and delirium but not with single use (3). Our patient used only dexamethasone 8 mg IV before each chemotherapy administration for premedication. Thus, steroid induced mania is unlikely for the presented case.

CONCLUSION

Finally, when we evaluated together with the previous two cases, we decided to diagnose 5-FU-induced Bipolar disorder manic episode with mixed features for our case. Although prevalence of 5-FU induced psychiatric disorders is very rare, clinicians should keep in mind that a neuropsychiatric or mood disorders may be encountered during 5-FU treatment. The possible onset mechanisms are not known, however, further accumulation of these rare cases may explain the pathological mechanisms underlying bipolar disorders in cancer patients.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports

Gulcin Elboga ORCID: 0000-0003-3903-1835

Perihan Gizem Aksoy ORCID: 0000-0003-2304-333X

Tulay Kus ORCID: 0000-0001-5781-4820

Elif Karayagmurlu ORCID: 0000-0001-6530-4687

Gokmen Aktas ORCID: 0000-0003-4199-6943

Sengul Sahin ORCID: 0000-0002-5371-3907

Abdurrahman Altindag ORCID: 0000-0001-5531-4419

REFERENCES

1. Derogatis LR, Morrow GR, Fetting J, et al. The prevalence of psychiatric disorders among cancer patients. *Jama* 1983;249:751-7.
2. Gopalan MR, Karunakaran V, Prabhakaran A, et al. Prevalence of psychiatric morbidity among cancer patients—hospital-based, cross-sectional survey. *Indian J Psychiatry* 2016;58:275-80.
3. Brown ES, Chandler PA. Mood and cognitive changes during systemic corticosteroid therapy. *Prim Care Companion J Clin Psychiatry* 2001;3:17-21.
4. Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. *Sports Med* 2004;34:513-54.
5. Fora A, Alabsi E, Fakih M. A Case of 5-Fluorouracil–Induced Acute Psychosis. *Clin Colorectal Cancer* 2009;8:166-8.
6. Pacchiarotti I, Mazzarini L, Pellegrini P, et al. A case of manic episode during treatment with 5-fluorouracil, epirubicin and cyclophosphamide for breast cancer. *Gen Hosp Psychiatry* 2007;29:461-3.
7. Brieger P, Marneros A, Wolf H, et al. Manic episode in an ifosfamide-treated patient. *Gen Hosp Psychiatry* 2000;22:52-3.
8. Kerdudo C, Orbach D, Sarradet JL, et al. Ifosfamide neurotoxicity: an atypical presentation with psychiatric manifestations. *Pediatr Blood Cancer* 2006;47:100-2.
9. Acharya G, Cruz Carreras MT, Rice TW. 5-FU-induced leukoencephalopathy with reversible lesion of splenium of corpus callosum in a patient with colorectal cancer. *BMJ Case Rep* 2017;2017:pil:bcr-2017-222030.
10. Niemann B, Rochlitz C, Herrmann R, et al. Toxic encephalopathy induced by capecitabine. *Oncology* 2004;66:331-5.
11. Yeh K, Cheng A. High-dose 5-fluorouracil infusional therapy is associated with hyperammonaemia, lactic acidosis and encephalopathy. *Br J Cancer* 1997;75:464-5.
12. Rundell JR, Wise MG. Causes of organic mood disorder. *J Neuropsychiatry Clin Neurosci* 1989;1:398-400.
13. Goodwin GM. Aromatase inhibitors and bipolar mood disorder: a case report. *Bipolar Disord* 2006;8:516-8.