CASE REPORT

Secondary mania following cancer chemotherapy with capecitabine

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SUMMARY

Mania-like states occurring due to neurological, metabolic or toxic conditions, without a primary mood disorder have been reported in scientific literature as secondary mania. A major clinical problem in such situations often stems from the difficulty to understand if the mood disturbance is indeed secondary to an organic cause or a coincidental primary mood disorder. Chemotherapy regimens have been associated with multiple psychiatric complications, including psychosis, mania and anxiety. Capecitabine is implicated to be associated with encephalopathy whose clinical presentation often mimics that of psychosis. However, presentations with mania have not been reported until with the capecitabine and oxaliplatin combination chemotherapy regimen. In this report, we describe a case of secondary mania in a patient suffering from carcinoma colon on treatment with chemotherapy regimen of capecitabine and oxaliplatin.

BACKGROUND

Cancer chemotherapy for carcinoma colon involves use of capecitabine and oxaliplatin as one of the first line agents. The effects of such medications are known to have significant adverse neurological and psychiatric sequelae.^{1–7} This case shows that there is possibility of emergence of manic symptoms during chemotherapy and highlights the potential clinical implications to be considered for the long-term management of such presentations. In real-life situations, chemotherapy regimens often cannot be altered or stopped. A careful risk benefit analysis of all available options and strong liaison with other treating physicians managing medical and surgical aspects of cancer, focusing on overall betterment of quality of life, should be actively sought for management of such complicated cases.

CASE PRESENTATION

A 46-year-old man of middle socioeconomic status, holding a managerial position in a private firm, was referred to the psychiatry department by the treating oncologist in view of emergence of behavioural symptoms during the third cycle of chemotherapy. Four months prior to the referral, the patient had been diagnosed with stage 3C carcinoma colon and was treated with a combination of surgical resection and chemotherapy. A colectomy with diversion ileostomy had been performed and his chemotherapy included a combination of capecitabine and oxaliplatin given in monthly cycles. During the end of the third week

of the third chemotherapy cycle, the patient started showing irritability, anger outbursts, overtalkativeness, decreased need for sleep, increased goal directed activity, increased appetite, heightened self-esteem and over-religiosity, all of which increased over the next 10 days when psychiatric referral was sought and the patient was admitted to inpatient psychiatric ward for management. Detailed evaluation ruled out any history of psychiatric illness or any evidence of psychiatric disorder in his first-degree relatives, indicating towards a possibility of secondary mania. Physical examination revealed a frail built man with a body mass index (BMI) of 14.36 kg/m² and blood pressure of 94/60 mm Hg. Mental status examination showed a conscious, alert and oriented person with increased psychomotor activity. There were no fluctuations in his consciousness or sun-downing or perceptual abnormalities. Patient's speech was increased in productivity, and he showed elated affect, increased self-esteem and prolixity in thought. He had poorly sustained attention and concentration with impaired judgement and absent insight. Young Mania Rating Scale (YMRS) at admission showed a score of 31, suggesting a severe manic episode. At the time of current presentation, the patient had normal serum electrolyte levels with normal blood counts, liver function, kidney function, blood sugar, lipid profile, thyroid profile, urine screen for morphine and cannabis was negative, chest X-ray and ECG were within normal limits.

History revealed that during the first drug-free day after the previous (1 month before current presentation) second cycle, the patient had developed transient agitation, big plans, ideas of grandiosity and altered sensorium and disorientation lasting for a day, suggestive of delirium. Blood investigations at that point had revealed hyponatraemia (115 mmol/L). These symptoms remitted after correction of serum electrolyte levels.

INVESTIGATIONS

Serum electrolytes and other biochemical parameters were found to be within normal range. MRI brain during the event showed features suggestive of mild cerebellar and cerebral atrophy and calcification in bilateral basal ganglia region, which did not explain the acute presentation of the patient.

DIFFERENTIAL DIAGNOSIS

According to International Classification of Diseases 10th Revision: F30.1 Mania without psychotic symptoms.

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TREATMENT

The patient was treated with tablet olanzapine, in dose up to 20mg/day along with tablet clonazepam as required for sleep. With treatment, patient's sleep, appetite, self-care and care of ileostomy improved within the first 2 days. However, the patient continued to have a cheerful mood with ideas of increased self-esteem and occasional anger outbursts over the next 3 weeks, which resolved by the fourth week when he was discharged from inpatient care to be followed up in the outpatient department (OPD). His YMRS score at discharge was 3 and his BMI increased to 16.8 kg/m².

OUTCOME AND FOLLOW-UP

The Naranjo Adverse Drug Reaction Scale revealed a score of 4, indicating a 'possible' causal association between chemotherapy and the manic presentation. Consultations with medical oncology department resulted in substitution of capecitabine with 5-fluorouracil from the next chemotherapy cycle due to possibility of drug-induced mania by capecitabine. After 3 weeks during the next chemotherapy cycle, the patient tolerated the new regimen well, and there were no further signs of affective disturbances during or after the subsequent cycles. The patient was followed up in the psychiatry OPD for the next 6 months until the completion of chemotherapy and is currently under regular follow-up with a plan to taper and stop his psychotropic medications.

DISCUSSION

To the best of our knowledge, this is the first report of mania occurring secondary to treatment with capecitabine and oxaliplatin. Although the patient was on a combination of capecitabine and oxaliplatin treatment, the absence of re-emergence of manic symptoms after restarting of chemotherapy with a regimen that included oxaliplatin suggests capecitabine to be the probable agent inducing manic change in this patient. However, the absence of manic symptoms over the next cycles might also be attributable to the cover of olanzapine, thereby preventing definite identification of the causal agent between these two drugs.

A few case reports have highlighted occurrence of capecitabine-related reversible encephalopathy leading to sensorimotor dysfunction, altered mental status, memory deficits, headaches, ataxia, dysarthria and epilepsy-like symptoms.^{6,7} However, there are no available reports of any psychiatric adverse effects in literature, relating to capecitabine therapy alone or subsequent to capecitabine and oxaliplatin (combination) chemotherapy regimen.

Incidentally, the alternate regimen started in our patient consisting of 5-fluorouracil (5-FU) and oxaliplatin have more reported neuropsychiatric adverse effects than capecitabine and oxaliplatin (combination), which led to the clinical decision of continuing olanzapine for the whole course of chemotherapy rather than discontinuing it after stopping capecitabine. 5-FU-related adverse effects comprise cerebellar manifestations of ataxic gait, dysmetria, nystagmus and scanning speech; focal weakness and limb paralysis and neuropsychiatric symptoms of confusion, disorientation and memory loss in up to 5% cases.⁸ Visual hallucinations, bizarre behaviour and agitation have been occasionally reported.³ 5-FU and oxaliplatin are also associated with posterior reversible encephalopathy syndrome characterised by headaches, altered mental status, seizures and visual loss.⁹

The absence of manic symptoms during the first two cycles with capecitabine seemingly contradicts a conclusion of

drug-induced mania. However, even the well-established adverse effects of these chemotherapeutic agents (described above) typically occur for the first time during the second or third cycle in almost all reports or even as late as the sixth cycle in some instances,⁷ thereby suggesting that the side effects of these drugs might be cumulative or delayed. Moreover, mania-like symptoms did appear during the second cycle, although there remain some doubts as to whether they represented a manic episode or delirium. The possibility of the latter certainly exists considering the coexistence of hyponatraemia and low BMI in this patient.

A final issue to be highlighted in such cases is difficulty in differentiating between secondary mania and a primary mood disorder. In this patient, the first episode of an affective nature occurring at 46 years of age, with acute onset and rapid resolution, in absence of family history of psychiatric disorders and with absence of any other neurological signs and symptoms or abnormal laboratory test results (suggesting alternative causes) strongly suggests secondary mania to be the most probable case rather than a primary mood disorder.

Stress of a cancer diagnosis and the associated complex treatment have also been reported as precipitants of mood (including manic) episodes.¹⁰ However, in this case, the diagnosis of cancer was made 5 months back, followed by major surgical intervention 4 months ago without the development of any mood disorder, thereby making stress an unlikely cause for the current manifestation.

This report highlights the possibility of emergence of manic symptoms during chemotherapy and discusses the potential clinical implications to be considered for the long-term management of such presentations. In real-life situations, chemotherapy regimens often cannot be altered or stopped. A careful risk benefit analysis of all available options and strong liaison with other treating physicians managing medical and surgical aspects of cancer, focusing on overall betterment of quality of life, should be actively sought for management of such complicated cases.

Learning points

- ▶ Secondary mania can be caused/precipitated by cancer chemotherapeutic agents like capecitabine.
- ▶ Differentiating between secondary mania and a primary mood disorder is often challenging.
- ▶ Effective liaison between different specialist departments is warranted for timely identification and management of such cases.

Contributors The authors have jointly collected the data and drafted the case report and share the responsibility of accuracy of its contents. HG was responsible for compilation of the data, conducting relevant review of literature and preparing the draft proposal of the case report. SP edited the draft proposal, compiled the analysis and interpretation of review of literature and the discussion, highlighting the relevance of the case. KSD conceptualised the case and designed the report after critical review of the proposal, along with supervision of the work of previous two authors. RC is the team lead and supervised all the other authors in critically analysing and drafting the report to meet the desired excellence.

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