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5-FLUOROURACIL INDUCED GENERALISED TONIC-CLONIC SEIZURES IN COLO-RECTAL CARCINOMA: CASE REPORT

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ABSTRACT
The fluorinated pyrimidine 5-Fluorouracil acts as a frontline combination treatment of metastatic colorectal cancer. In advance disease state of cancers the combination chemotherapy regimens such as 5-FU based chemotherapy along with the necessary vitamin caleucovorin and novel cyotoxic agent Oxaliplatin have developed increase in overall survival and disease free state, but at the risk of toxicities. The formation of the intermediary metabolites of 5-FU i.e., fluorocitrate or fluoroactate directly inhibits the krebs tricarboxylic cycle and subsequently affects the destruction of ATP-dependent urea cycle. This results in hyperammonemia causing neurotoxicity such as generalized tonic-clonic seizures. Although neurotoxicity is a rare side-effect of 5-FU, its occurrence may be worrisome and preclude further administration of this vital drug. Here we report on a rare or uncommon adverse drug effect of 5-fluorouracil induced generalized tonic-clonic seizures. A 28 years-old Male patient was diagnosed with advance stage of colo-rectal cancer (CA colon) and was started with combined chemotherapy regimen of (MFOLFOX)6. On second day treatment with 5-FU continuous I.V infusion over 23hours patient experienced drug induced convulsions as generalized tonic-clonic seizures. Treatment was given with anti epileptic drug and I.V fluids and treatment for CA colon was planned with CAPOX later to avoid 5-FU.

KEYWORDS: Colorectal cancer, 5-Flurouracil(5-FU), Neurotoxicity, Genaralised-tonic-clonic seizures, Hyperammonemia.

INTRODUCTION
Worldwidepopulation is increasing and simultaneously disease conditions are equally increasing in challenging manner. Among all the life threatening diseases cancer stands on the top priority list giving a tough battle with the life along with the other related conditions.[1] From the different types of cancers colorectal cancer (CRC) is formidable health concern world-wide. Indian council of medical research (ICMR) conducted a survey in 2014 and publish its report stating that colorectal cancer is the third most common cancer in men (663000 cases, 10.0% of all cancer cases) and the second most common in women (571000 cases, 9.4% of all cancer cases) in India.[2]

In order to treat this kind of life threatening cancers different type of treatments are applied such as surgery, chemotherapy, radiation, immunotherapy and hormonal-therapy. Sometimes these are combined and tailored for targeted treatment or treated differently one after the other depending on the cancer type and severity.[1]

In this present case report presentation patient was treated with surgery followed by the chemotherapy. Even though selectivity of majority of drugs is limited and involves the most toxic drugs in the therapy it is considered as a systemic therapy, which may also affect the whole body.[1] The main aim of chemotherapy drugs or anticancer drugs is to target rapidly developing cancer cells, but they can also affect healthy cells that grow rapidly.[1] The effect of these chemotherapy drugs on both cancer and healthy cells often leads to adverse drug reactions and side effects.[1]

In our patient case the (MFOLFOX)6 combination was used to treat the colorectal cancer (CA colon). This combination includes 5-Fluorouracil, Calci-leucovorin and Oxaliplatin.

CASE REPORT
A 28years-old male patient was diagnosed with advance stage of Colo-rectal carcinoma (CA colon) and underwent surgery. Later he had complains of vomiting and altered bowel movements for two months and visited

to the hospital for check-up and got admitted in the hospital for Colo-rectal cancer (CA colon) treatment. His pre-existing medical conditions revealed that patient had no medical conditions of neurological, respiratory, cardio vascular, CNS related problems, no medical history of seizures were reported. patient condition was normal as Afrebrile, Vitals-stable, B.P-120/80mmHg, PR:102/min, Before start of the chemotherapy following lab investigation were done for the patient such HIV1&2 - non-reactive, HBsAg- negative, CBP - normal; serum albumin - 4.5 mg/dI (normal range: 3.5-5.0mg%), serum total bilirubin-0.6mg/dI (normal range: 0.2-1.0mg/dI), serum S.G.P.T -40 (normal range: 5-40IU/L). After the lab test results were normal. He was started on a combination chemotherapy regimen of 5-FU, Oxaliplatin and Caleucovorin as (MFOLFOX)6. 5-FU dose was 700mg I.V bolous/stat and 5-FU at 2gm continuous I.V infusion over 23 hours, Oxaliplatin dose 150mg I.V, Caleucovorin dose 700mg. After administration and completion of First day of combination chemotherapy regimen patient was normal with no signs and symptoms of adverse drug reactions. But on second day of combination chemotherapy regimen at 12:30pm during the 5-FU 2gm in 30ml normal saline over 23-hours continuous I.V infusion administration, he developed cognitive disturbances, loss of consciousness, convulsions for seconds timewith no history of headache as ADR, at 5.15pm he again complained of stiffening in the body, confusion and jerks of the body was shown, one episode of vomiting was reported. So the 5-FU 2gm as continuous I.V infusion was withdrawn completely and he was treated with zofer-8mg, Decadran -8mg, injection Diazepam 10mg I.V slowly, Eptoin I.V injection 100mg, I.V fluids, Eptoin I.V injection 15mg in 100ml normal saline over 15-20mins, Calcium 500mg tablets. The lab report after the second day combined chemotherapy regimen revealed that the Serum Total Biluribin and S.G.P.T was elevated compared with the normal range as Serum Total Biluribin – 2.9mg/dI and S.G.P.T as 61mg/dI. The EEG was normal. Patient was referred to MRI scan. The outcome of ADR was recovered and the patient was discharged and chemotherapy was planned with CAPOX later to avoid 5-FU. In the present case, the patient was not on concomitant medications.

DISCUSSION

In case of localized Colo-rectal cancer surgical resection is the main treatment modality, but more than 40% of patients with stage II and III CRC will even though develop disease recurrence within 5 years of initial diagnosis.[4, 5,6] Thus, to eradicate occult micro-metastatic disease and to reduce the risk of disease recurrence adjuvant systemic chemotherapy is recommended in high-risk patients.[4,6]

5-FU which is fluorinated pyrimidine belongs to the family of drugs called anti-metabolite and anti-neoplatic agent was first launched in 1958 and still continues as the keystone of recent adjuvant chemotherapy protocols in CRC of FOLFOX regimens and Mayo.[4]

In advance disease state of cancers the combination chemotherapy regimens such as established 5-FU based chemotherapy along with the necessary vitamin caleucovorin which enhances the anti-cancer effects and the recently introduced platinum based anti-neoplastic novel cyotoxic agent Oxaliplatin have developed overall increased survival and disease free state, but at the risk of increasing toxicities.[4,6,7]

Common adverse effects and reactions of 5-FU are gastrointestinal toxicities such as nausea, vomiting, stomatitis, and diarrhoea. Hematologic effects are bone marrow suppression leading to neutropenia and infections. Leukopenia may be less severe with the continuous infusion therapy thrombocytopenia .Dermatological reactions such as skin rash and itching. The other adverse rare effects are photophobia, lacrimation, cardiac toxicity and neurotoxicity.[4,7,8]

The administration of 5-FU can root to both delayed and acute neurotoxicity.[11] The delayed neurotoxicity generally presents as a sub-acute multifocal leukoencephalopathy and the acute neurotoxicity is related to dose and usually self-limiting epitomised as encephalopathy or as cerebellar syndrome which is reversible such as Generalised tono-clonic seizures (GTCS) as seen in this particular case or in our patient, are uncommon and have rarely been reported.[4,8,12] According to the literature reviews different mechanisms for such neurotoxicity have been suggested because the underlying accurate mechanism is difficult to understand.[4,8,11,12,13]

Among these hypothesis some researchers consider that the responsible factor for Neurotoxicites are non-specific immune-mediated process[4,7,11] and the others indicated a more simple type in which the end product of 5-FU metabolism i.e., ammonia accumulates in large quantity after either high-dose of I.V bolus injection or a continuous I.V infusion administration of 5-FU.[4,7,8 ,9,10] Usually this ammonia is cleared by ATP-dependent urea cycle but the intermediate product of 5-FU i.e., the fluorocitrate or fluoroactate directly inhibits the kerbs tricarboxylic cycle and subsequently affects the destruction of ATP-dependent urea cycle.[4,7, 8,9] This results in hyperammonemia causing neurotoxicity inducing GTCS.[4,7,10,11]

The main diagnostic criteria for 5-FU induced GTCS (neurotoxicity) in this case includes such as 1) the main supporting evidence of no pre-existing medical history or condition of seizures, epilepsy, other neurological problems, cardiac related problems in the patient prior to 5-FU administration. 2) Occurrence of GTCS during the continuous administration of 5-FU I.V infusion over 23 hours. 3) Inclusion of elevated levels of serum total biluribin and S.G.P.T levels after the administration of

continuous i.v infusion of 5-FU but exclusion of other metabolic or physical aspects that could have an effect the level of consciousness like electrolyte imbalance, hyperglycemia, hypoglycaemia, azotemia, sepsis and brain metastasis[4,7,8,12] 4) exclusion of other drug effects by concomitant medications. By considering all above mentioned parameters and positive de-challenge according to the WHO causality assessment scale the time taken for the onset of reaction with the suspected 5-FU induced GTCS was probable.

CONCLUSION

Withdrawal of 5-FU continuous I.V infusion is the main step in the initial treatment of 5-FU induced GTCS.[4, 10, 11, 12] Even though many literature studies have suggested different treatment methods ranging from use of supportive measures like either corticosteroids or thiamine as single or in combination regimen, have shown no reliable efficacy.[4, 10,11, 12] Treatment with anti-epileptic drugs, I.V fluids and calcium tablets resulted in timely symptomatic recovery in our patient. Thus finally it can be concluded that generalised tonic-clonic seizures (neurotoxicity) is although uncommon (<1%) and rare is significant complication and has to be noted as key point when treated with 5-FU chemotherapy agent alone or in combination with otherdrugs.[4, 7,8,11,12] Though the recovery is complete and mentioned ADR is just temporary, clinicians should be aware and should be more careful in patients with already pre-existing medical condition of neurologic problems.[4, 7, 11]

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