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Case Report

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Reversible Toxic Encephalopathy related to Treatment with Capecitabine: A Discussion about Chemotherapy-Induced Neurotoxicity and a Case Report

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Abstract

Introduction: Capecitabine is a chemotherapeutic widely used in current medical practice, quickly replacing 5-Fluorouracil in the treatment of certain cancers. Although it is rarely encountered, neurotoxicity is an adverse effect that should not be neglected, especially if elderly patients are involved.

Case: An 82-year-old patient, diagnosed with digestive neoplasm, currently being treated with Capecitabine, is brought to the emergency room by her family for an acute confusional episode and speech disorder. Brain imaging is performed, which does not identify significant lesions, and biological tests exclude major imbalances that would explain the neurological dysfunction. Stopping the chemotherapy treatment determines the rapid resolution of the symptoms. Thus, the diagnosis of toxic encephalopathy is made and it is decided to definitively stop treatment with Capecitabine.

Conclusion: These being presented, whenever there is an alteration of the neurological status during treatment with Capecitabine, Reversible toxic encephalopathy should be considered. This drug remains a preferred chemotherapy in current practice, but the adverse neurological effects should not be neglected, especially for the population at risk.

Keywords: Neurotoxicity; Capecitabine; Dihydropyrimidine dehydrogenase; Encephalopathy.

Introduction

The adverse effects of chemotherapy on the Central Nervous System (CNS) are widely known; These can manifest under a variety of neurological syndromes such as acute, subacute, chronic encephalopathies, cerebellar dysfunction, cognitive dysfunction, reversible posterior encephalopathy, myelopathies or even meningitis [1]. Certain chemotherapy drugs are often associated with neurotoxicity such as Ifosfamide, Methotrexate, but also 5-Fluorouracil (5-FU), especially in high doses [2].

Capecitabine is a precursor of 5-FU, which it quickly replaced in the last 20 years, especially in the treatment of gastrointestinal or breast cancers, due to the oral route of administration, considered easier for elderly oncology patients [3].

Capecitabine, a fluoropyrimidine carbamate, was designed with the exact aim of delivering 5-FU selectively to tumor cells, being initially metabolized in the liver and later, in the final stages of transformation, in the tumor cells. This compound is initially absorbed intact, being then metabolized into the final product in the form of 5-FU with cytostatic action in three stages; As a first

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step, under the action of hepatic carboxylesterase, capecitabine is transformed into 5'-deoxy-5-fluorocytidine, which will later become 5'-deoxy-5-fluorouridine under the influence of cytidine deaminase found in the liver and in tumor cells. In the third stage, 5'-deoxy-5-fluorouridine is converted into 5-FU with the help of thymidine phosphorylase, the enzyme whose activity has been shown to be significantly higher in tumor formations than in healthy body tissues. Thus, due to the fact that this metabolic chain occurs mainly in tumor tissue, capecitabine has the advantage of minimal toxic exposure of healthy tissue with maximum targeting of the active substance to the targeted pathological formation [4,5].

Encephalopathy caused by 5-FU is often mentioned in medical literature, however, in the case of Capecitabine, only a few cases of neurotoxicity have been documented; In most cases found, the symptoms disappeared shortly after stopping the medication, with the help of conservative treatment. Variants of mutations in Dihydropyrimidine Dehydrogenase (DPD), a liver enzyme that facilitates the elimination of 5-FU metabolites, may explain the toxic effects of Capecitabine. Although the relationship between DPD deficiency and Capecitabine neurotoxicity could not be confirmed in all cases, enzyme testing is recommended to be done, especially in the case of elderly patients [6,7].

Case report

The 82-year-old patient, diagnosed with stage pT3pN0Mx sigmoid colon adenocarcinoma, for which she underwent a surgical intervention approximately two months ago, currently being treated at home with Capecitabine 4 g/day, is brought to the emergency room by her family for an episode of confusion. This symptomatology started approximately 12 hours before presentation, when the patient called her relatives in the middle of the night to have a simple conversation; Following that, in the morning of the same day, her niece found her wearing sunglasses at home and trying to talk on the phone holding the device to the nose. The relatives state that this episode occurred suddenly, in apparent good health, the patient having a normal behavior the day before the presentation to the emergency room. From the patient's history, we note that she was diagnosed 4 years ago with a malignant jejunal tumor, for which she was treated with Capecitabine. Neurological examination performed at the time of presentation reveals a confused patient, with difficult cooperation, disorientated temporospatially, who partially executes simple commands, does not execute complex commands, does not respond adequately to questions, with echolalia but without motor deficit and with symmetrically deep tendon reflexes.

Routine blood tests performed at the emergency department showed a mild lymphopenia with no signs of infection, myelosuppression, electrolytic disturbance, renal or hepatic impairment.

Cerebral computed tomography performed, without and with contrast, does not reveal pathological tomodenstiometric lesions of an acute nature, nor pathological intakes of the gadolinium substance. The patient remains under observation in the neurology department, and in the following hours, after stopping the chemotherapy treatment and under intense hydration, the patient's condition improves rapidly, with the remission of the confusional syndrome and the language disorder in less than 24 hours.

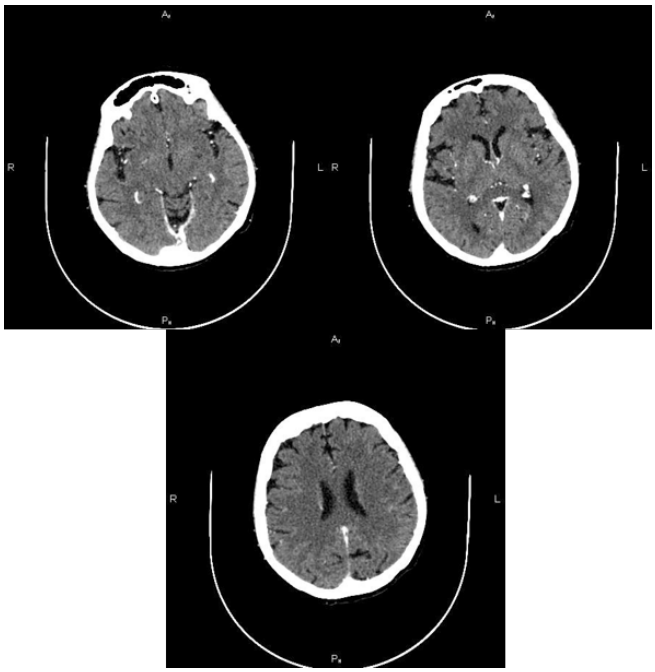

Figure 1: Cerebral computed tomography whitout evidence of focal lesions and no enhancement upon gadolinium administration.

Thus, after 48 hours from the onset of the symptoms, a brain MRI was performed, which did not reveal signal abnormalities, but only a few demyelinating lesions at the level of the bilateral frontal lobes, with a microangiopathic substrate and no enhancement upon gadolinium administration was observed.

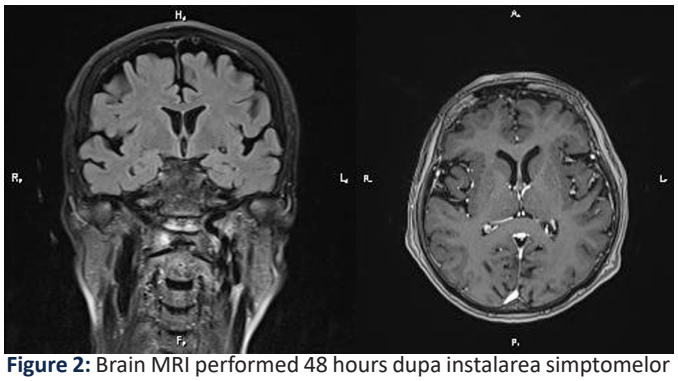

Figure 2: Brain MRI performed 48 hours dupa instalarea simptomelor with no pathological findings.

With the high suspicion of a toxic effect of capecitabine, the patient was tested for the most prominent mutations of the DPD gene (variant DPYD E412E (HapB3), variant DPYD I560S (*13), variant DPYD IVS14+1G>A (*2A), variant DPYD D949V) who came out negative a few days later. The attending oncologist is contacted and it is decided, with the patient's consent, to stop treatment with Capecitabine.

The patient was reevaluated one month later without any pathological changes being detected during the neurological examination. She is still under oncological supervision and no other line of chemotherapy was prescribed in her case.

Discussion

Capecitabine is an oral chemotherapy, which is becoming more and more popular these days, being preferred instead of its precursor, 5-FU, due to the easy way of administration [8].

The encephalopathy caused by 5-FU has many ways of presentation such as states of confusion, behavior disorders or seizures, the diagnosis being based on the following criteria [9]:

- Appearance of signs and symptoms during treatment or shortly after completion of treatment.
- Exclusion of other causes that could explain the patient's symptoms, such as hypo- or hyperglycemia, altered serum electrolyte levels, liver failure, sepsis, azotemia or CNS neoplasms.
- Exclusion of adverse effects determined by concomitantly administered medication.

Despite its widespread use in medical practice, little information is known about the toxicity of Capecitabine on the CNS, being only a few cases published in the literature. Cases of induced CNS toxicity manifested by memory disorders, episodes of confusion, psychiatric disturbances, ataxia, speech disorder such as dysarthria, or even seizures have been described [10,11].

We present a case of reversible toxic encephalopathy, due to treatment with capecitabine, which appeared on the eighth day of administration, being the second cycle of treatment with this chemotherapy in the patient's life. Published material report latency period until the installation of the clinical picture which varies between 3 days to 3 months after the initiation of this treatment [9].

Brain imaging, especially brain MRI, varies from none to changes in the white matter, most of the time in both cerebral hemispheres [6,9]. In the present case, brain imaging did not identify pathological changes that could be correlated with the patient's symptoms, but the investigation was carried out more than 48 hours after the onset of the symptoms and after stopping the treatment.

Regarding the etiopathogenic mechanism, several hypotheses have been launched that must be analyzed. Starting from the known fact that 5-FU toxicity is significantly higher among the female population, Manuela Fantini et al, in a literature review published in 2010 [6], she launches the hypothesis according to which toxicity could be caused by DPD deficiency. Although the relationship with enzyme deficiency could not be demonstrated in all patients, its dosage is still recommended, especially in elderly patients. Testing for mutation of the DPD gene came out negative in the case of our patient. In addition, it is known that Capecitabine can penetrate the BBB, thus reaching the level of the CNS, where it can be metabolized into 5-FU, then manifesting its toxic effects at this level. Thus, the toxic effect of the substance on the vascular endothelium with the temporary alteration of the protective barrier of the nervous system must also be taken into account [9].

These being presented, whenever there is an alteration of the neurological status during treatment with Capecitabine, reversible toxic encephalopathy should be considered, especially in the case of elderly patients. The patients' clinic and imaging findings differ from one patient to another, the evolution being favorable, with the remission of symptoms shortly after stopping the treatment. Although it is a rare adverse reaction, it should not be neglected as additional tests are required. Thus, once this pathology is suspected, it is recommended to immediately stop the treatment with the application of the necessary supportive treatments, after excluding other causes that could explain the symptoms [12].

Capecitabine remains a preferred chemotherapeutic in current practice, but adverse neurological effects must be carefully monitored, especially for the population at risk.

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