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*Case Report: Capecitabine-Induced Multifocal  
Leukoencephalopathy masquerading as Stroke in a 40-  
year-old male with Nasopharyngeal Carcinoma*

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John Joshua Q. Punsalan, M.D., M.B.A.<sup>1</sup>, Marivic A. <sup>4</sup>Guieb-Preysler, M.D., F.P.N.A.<sup>2</sup>

<sup>1</sup>. Department of Neurosciences, Section of Neurology, Makati Medical Center,  
Amorsolo Street, Legazpi Village, Makati, 1229 Kalakhang Maynila, Philippines +63-  
9175244897; joshpunsalan.mmc@gmail.com

<sup>2</sup>. Department of Neurosciences, Section of Neurology, Makati Medical Center,  
Amorsolo Street, Legazpi Village, Makati, 1229 Kalakhang Maynila, Philippines

### **Abstract**

*A 40-year-old male diagnosed with Nasopharyngeal Carcinoma St. IV undergoing chemo and radiotherapy was referred to our service because of sudden right upper extremity weakness. He had been started on Capecitabine 9 days prior to consult. A cranial MRI revealed bilateral and symmetric diffusion restriction over the centrum seimovale, corona radiata, internal capsule, cerebral peduncles. An acute leukoencephalopathy was considered, prompting discontinuation of capecitabine. Symptoms improved after 24 hours of discontinuation. Leukoencephalopathies among chemotherapeutic agents have been well-documented. Capecitabine has just recently gained prominence due to its more favorable safety profile and its side effects are less known. High index of suspicion through knowledge of all possible side effects is important, since symptoms commonly resolve upon discontinuation of the medication.*

**Keywords:** *Acute Leukoencephalopathy; Capecitabine; Neurotoxicity; Chemotherapy*

### **Introduction**

Chemotherapy for malignant tumors continues to evolve. As such, recognizing

the side effects of chemotherapy along with its curative effects is vital in clinical practice. Capecitabine , a precursor of 5-

fluorouracil (5-FU), is an oral fluoropyrimidine cytotoxic agent developed with the aim of providing a more effective and less toxic alternative to 5-FU. It is an orally-administered prodrug that converts preferentially to 5-fluorouracil (5-FU) within tumors, resulting in enhanced concentrations of 5-FU in tumor tissue. Given that it targets tumor tissue directly, capecitabine was expected to reduce the risk of side effects associated with fluoropyrimidine.

Capecitabine itself is not cytotoxic, but it becomes effective after it has been converted to 5-FU in tumor cells. It is widely used because it can be orally administered and is associated with fewer side effects. However, as the use of capecitabine becomes more widespread, its side effects appear to be similar to those of 5-FU.

Cerebral Leukoencephalopathy is a rare but serious side effect of 5-FU with a wide variety of symptomatic presentation. Radiologic presentations appear to be more consistent than the symptomatology and will be discussed further in this paper. Very few cases of capecitabine-induced cerebral leukoencephalopathy have been reported.

### **Case Presentation**

A 40-year-old right-handed male came in due to right upper extremity weakness. He is a diagnosed case of Nasopharyngeal Carcinoma St. IV undergoing chemo- and radiotherapy.

He underwent 35 cycles of radiotherapy and 2 cycles of Cisplatin treatment. The last dose of Cisplatin was given ten days prior to consult. He was started on Capecitabine at 3.5 grams per day nine days prior to consult. Six days prior to consult, he experienced acute-onset left-sided weakness lasting less than 24 hours with spontaneous resolution. Four days prior to consult, he experienced acute-onset non-progressive right upper extremity weakness described as heaviness of the right arm. No headache, no dizziness, no slurring of speech, no sensorial changes. Persistence prompted consult and subsequent referral.

Contrast MRI showed symmetric areas of non-enhancing, restricted diffusion signals involving both centrum semiovale and corona radiata, both posterior limbs of the internal capsules extending to the bilateral crus cerebri (bilateral corticospinal tract), and the corpus callosum.

Given the temporal profile of chemotherapeutic intake, presentation of neurological symptoms, and the distinct MRI findings, a provisional diagnosis of Capecitabine Induced Multifocal

Leukoencephalopathy was determined, so Capecitabine was discontinued. Symptoms resolved within 24 hours of discontinuation.

### **Discussion**

Capecitabine is an oral fluoropyrimidine chemotherapeutic agent commonly used in the treatment of pancreatic, colorectal, and breast cancer.

Capecitabine-induced leukoencephalopathy was first described in 2004 by Niemann et al. Based on literature, it affects patients aged 40-82 years. This appears to affect females more, with a female to male ratio of 5:1. In the reported cases, Capecitabine was administered for colorectal, breast, and pancreatic malignancies.

To the authors' knowledge, this is the first reported case of Capecitabine Induced Leukoencephalopathy in the setting of Nasopharyngeal Carcinoma.

### **Pathophysiology**

Capecitabine undergoes a multi-step cascade to become the active product, 5-fluorouracil (5-FU), which inhibits thymidine synthesis and DNA replication.

The exact mechanism of Capecitabine-induced neurotoxicity has yet to be determined.

It is important to note, however, that its intermediate metabolite,  $\beta$ -deoxy-5-fluorouridine ( $\beta$ -DFUR), has demonstrated the ability to cross the blood-brain barrier. Thymidine phosphorylase, the last enzyme in the cascade of Capecitabine conversion to 5-FU, has been found more commonly in the white matter tracts. This may explain the predilection of lesions within these regions. Studies have shown that 5-FU can cause acute or delayed damage to myelinated tract of the central nervous system.

### **Clinical Presentation**

Reported symptoms in cases of capecitabine-induced leukoencephalopathy range from mild ones such as nausea to more severe ones like dysphasia, seizures, sensorial changes, and cerebellar syndromes. Weakness in these cases tend to be generalized, but one case had unilateral weakness as well. Symptoms tend to occur as early as 3-7 days to as late as 1-2 months after drug initiation.

### **Radiographic Findings**

Case reports have featured cerebral white matter changes on Magnetic Resonance Imaging (MRI), particularly diffusion restriction and/or increased signal intensity on T2/FLAIR sequences. Commonly observed in previous case reports are

symmetrical periventricular high signal intensities in diffusion and T2-weighted images with corresponding drops in ADC.

Lesions tend to involve the corpus callosum, middle cerebellar peduncles, areas of white matter such as the subcortical, periventricular, posterior parietal, and anterior thalamic regions. MRI features seem nearly pathognomonic with bilateral and symmetric diffusion-restricting lesions of the centrum semi-ovale, corpus callosum, and corticospinal tracts.

### **MRI Findings**

DWI/ADC: Diffusion restriction

T2/T2FLAIR: May have increased signal intensity

CONTRAST: Non-enhancing

SYMMETRY/LATERALITY: Symmetric, bilateral

AREAS INVOLVED: Corpus callosum (commonly), subcortical periventricular, posterior parietal, anterior thalamic.

### **Management**

Withdrawal of the drug generally leads to improvement of neurological symptoms and full recovery within a few days. Excellent prognosis with minimal to no residual deficits has been reported in cases, as early as 1 day after chemotherapy

cessation. For less than half the case reports, follow-up imaging was done in 4 cases, revealing near complete resolution of the earlier detected imaging abnormalities. The benefit of steroids has yet to be established. A case report by Bougea et. al. (2015) showed that metronomic chemotherapy (reintroduction of treatment with lower doses) may be a safe choice, but this has yet to be replicated in other studies.

### **Conclusions**

Our patient was known to other services as a case of Nasopharyngeal Carcinoma. He was referred due to acute-onset neurologic deficits in the form of hemiparesis for which an acute stroke was considered. The MRI showed findings highly compatible with previous cases of capecitabine-induced leukoencephalopathy. In our review of literature, unilateral weakness was only seen in one other case. Ours had an alternating form of hemiparesis initially involving the left side transiently before recurring on the right, which prompted consult. Capecitabine has gained prominence due to its more favorable safety profile. This is why clinicians must be aware of its side effects, as rare as these may be, because increasing the index of suspicion will lead to earlier diagnosis and management. Given that cessation of the medication yields favorable outcomes,

pursuing knowledge regarding the side effects will be beneficial for patients receiving the drug. Like other encephalopathies, the symptoms here can be nonspecific. Some of them are suggestive of a generalized dysfunction, while some present with lateralizing signs easily mistakeable for stroke. However, the radiologic pattern: appearance on different sequences, structures affected, and presence/absence of contrast enhancement seem to be consistent among the case reports. Given the complexity of chemotherapy, clinicians must be equipped with as many therapeutic approaches as possible. This is why certain angles such as metronomic chemotherapy must be studied further as well. Granted the rarity of the case, it is imperative that clinicians learn as much as they can from each encounter and correlate such findings to the existing literature to fortify clinical knowledge on this condition and improve outcomes for cancer patients undergoing chemotherapeutic agents in general.

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