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Review

Subacute reversible toxic encephalopathy related to treatment with capecitabine: A case report with literature review and discussion of pathophysiology

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ABSTRACT

Introduction: Capecitabine, a 5-fluorouracil (5FU) pro-drug, is increasingly used in breast and gastrointestinal cancers due to its more convenient oral route of administration when compared to 5FU. Despite its widespread use, there are only a few reports on capecitabine CNS toxicity, while the pathogenic basis of such toxicity remains unclear.
Case: A 69-year-old male presented with recurrent generalized seizures 2.5 months after preoperative chemoradiotherapy with capecitabine in locally advanced rectal cancer. Brain MRI revealed a diffuse, subcortical white matter alteration suggestive of vasogenic edema. The diagnosis of toxic encephalopathy was supported after elimination of alternative causes of the neurological dysfunction and complete resolution of clinical and imaging findings after 3 months of no further chemotherapy.
Conclusions: Given the expanding use of capecitabine, physicians should be aware of this potential complication when a neurological worsening occurs during or after treatment with this chemotherapeutic agent. In our case, as in previously described cases encephalopathy was characterized by a favorable course after cessation of the drug. Vasogenic edema rather than cytotoxic edema may play a pivotal pathogenetic role in this form of encephalopathy.

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1. Introduction

Sporadic encephalopathy after systemic administration of conventional-dose chemotherapy has been reported for a variety of anticancer drugs (Hildebrand, 2006). Central nervous system (CNS) toxicity related to the chemotherapeutic agent 5FU is well-documented in the literature (Hildebrand, 2006; Han et al., 2008). It manifests as a cerebellar syndrome or as a subacute multifocal leucoencephalopathy with confusion, behavioral disorder, lethargy and seizures, most frequently seen in patients receiving 5FU in combination with levamisole. The diagnosis of 5-FU related encephalopathy includes following criteria: (1) development of encephalopathy during or shortly after completion of 5-FU administration, (2) exclusion of other metabolic or physical factors that may have an effect on the consciousness level, such as hyperglycaemia, hypoglycaemia, azotaemia, hepatic failure, electrolyte imbalance, sepsis and central nervous system involvement of cancers; and (3) exclusion of a drug effect by concomitant medications (Kwon et al., 2010).

Capecitabine, an oral prodrug of 5-FU, is another fluoropyrimidine rapidly replacing 5-FU in the treatment of breast and gastrointestinal cancers due to its more convenient oral route of

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administration when compared to 5FU. It is converted to 5FU by a cascade of three enzymes located in the liver and in tumors. Only a few cases of capecitabine CNS toxicity or capecitabine related encephalopathy are noted in the literature. A previous review reports 12 cases, added by a further case report (Videnovic et al., 2005), in all of which patients underwent complete regression of neurological symptoms after discontinuation of capecitabine.

2. Case report

A 69-year-old man, diagnosed with stage T3N1M0 rectal adenocarcinoma, without significant other morbidities, was admitted to our department because of a secondarily generalized tonic–clonic seizure starting on the left side of his body followed by a second generalized seizure later on the same day. One the previous day, he had an abrupt, transient sensory and motor dysfunction of the left arm without disturbance of consciousness. One week prior to this event, he had undergone abdominoperineal resection of cancer. Preoperatively, he had been treated with a neoadjuvant radiochemotherapy with capecitabine $2 \times 825\ mg/m^2$ p.o. from day 1 to day 30 and pelvic radiation therapy 45 Gy, 1.8 Gy from day 1 to day 30. The therapy was stopped 3 days earlier than initially planned due to radiation proctitis. Surgical resection followed 5 weeks after chemoradiation. No toxicities including myelosuppression were reported during radiochemotherapy. Neurological examination between the seizures showed a latent paresis of the left arm and leg with symmetrically brisk deep tendon reflexes, as well as a slight psychomotor retardation without any further abnormalities, MMSE score was 30/30.

Routine blood tests showed a mild sideropenic anemia, as well as a slightly elevated white blood cell count and CRP, with no signs

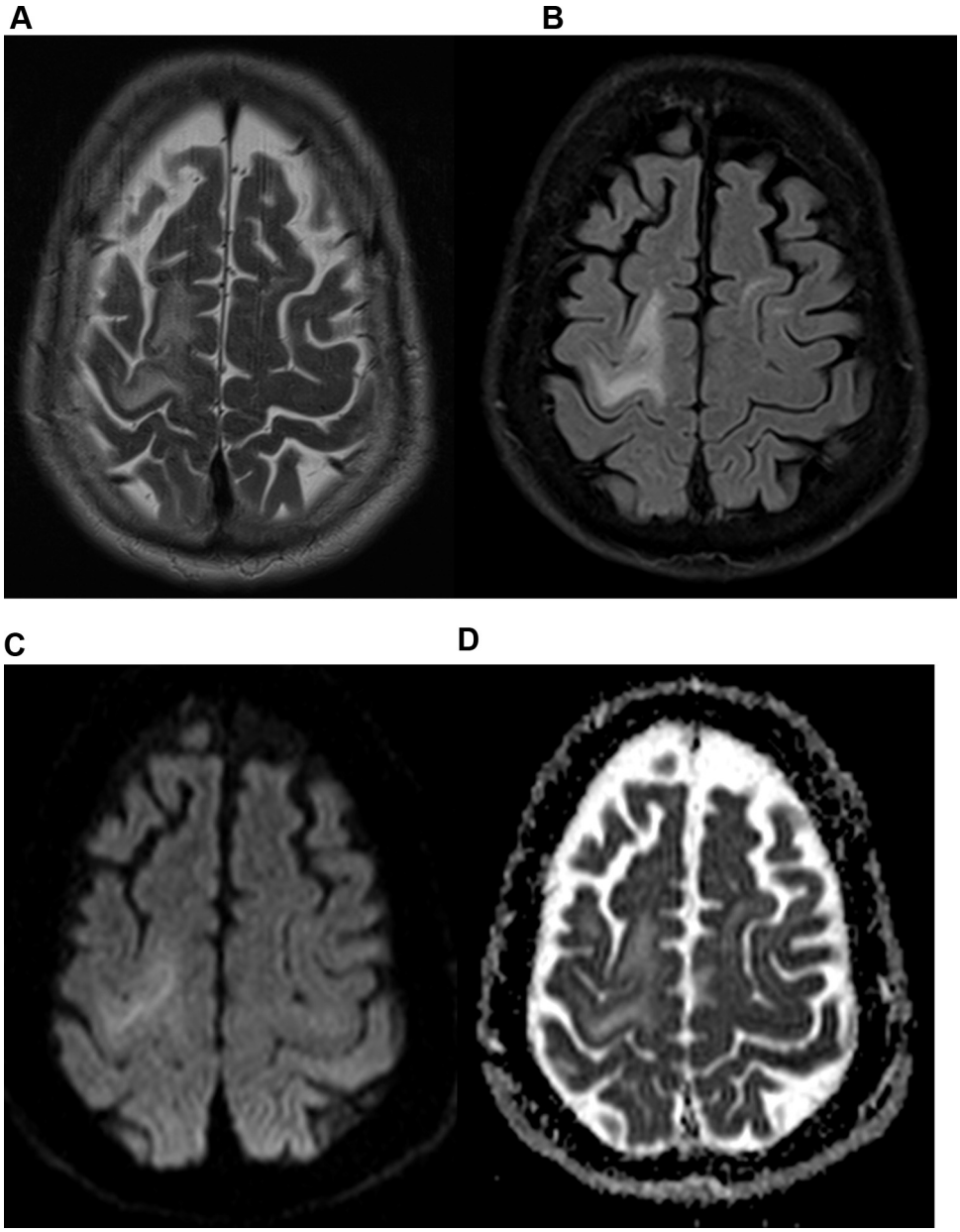

Fig. 1. (A, B) Brain MRI demonstrating diffuse, nonenhancing, hyperintense subcortical T2 and FLAIR-signal abnormality within the white matter of the right frontal lobe. There are also small lesions in the left frontal lobe. Lesions are confined to white matter sparing overlying adjacent cortical gray matter. (C) Reduced diffusion in sucortical white matter is seen on diffusion-weighted imaging (DWI). (D) Corresponding ADC maps show increased signal intensity suggestive of vasogenic edema.