To the Editor

5-Fluorouracil Induced Hyperammonemic Encephalophathy: Etiopathologic Correlation

Hyperammonemic encephalopathy (HE) attributable to 5-Fluorouracil (5FU) has been previously reported[1] although pathophysiology remains unclear. We describe a case of HE secondary to 5FU and we discuss the etiopathological correlation based on the brain postmortem findings.

A 59-year-old female with rectal adenocarcinoid lapsed into coma after a week of a chemotherapy regimen of Folinic Acid, 5FU and Oxaliplatin (FOLFOX). The patient had renal disease (creatinine: 1.7mg/dl urea: 62.2mg/dl) and Chronic Myeloid Leukaemia but no history of liver disease.

On admission, she was afebrile with stable vital signs. Neurological examination revealed a comatose patient with regular breathing pattern, small reactive pupils and ocular bobbing. No focal neurological deficits were found.

Blood count, serum electrolytes and liver function tests were normal. The only significant laboratory findings were increased creatinine (2.4mg/dl), urea nitrogen (74.8mg/dl) and ammonia (175.2µmol/L) levels. Cerebrospinal fluid was normal.

The electroencephalography showed global slowing with theta and frontal triphasic waves.

Brain computed tomography was normal. Magnetic resonance imaging (MRI) revealed diffuse cerebral edema and restricted diffusion in the bilateral cingulate cortex (Figure 1). The patient died and permission for the autopsy was obtained.

The macroscopic pathological study showed edema of the cingulate gyri (Figure 2A) and temporal lobes. At microscopical study, neuropil spongiosis, subpial (Figure 2B) and perivascular astrocytosis (Figure 2C) and Alzheimer glia type II could be seen (Figure 2D).

Discussion

The diagnosis of HE probably induced by 5FU was established based on the following criteria[1] (i) development of HE during or shortly after 5FU administration; (ii) exclusion of concomitant factors that may affect the conscious state as hypoglycemia, organ failure, electrolyte imbalance, sepsis and central nervous system involvement by cancer; (iii) exclusion of other drugs. This patient had renal disease therefore, a diagnosis of 5FU induced HE may not be irrefutable due to the impossibility to exclude the level of contribution of renal failure in the development of HE.

Hyperammonemia develops when ammonia is overproduced or/and inadequately removed. Primary causes including congenital defects in the urea cycle enzymes frequently debut in the neonatal period although late-onset urea cycle disorders have been reported. Secondary causes include liver and renal disease, urinary infection and drugs[2].

Although HE attributable to 5FU has been previously reported[1], pathophysiology remains unclear. Pharmacologically, 5FU is degraded to 5-fluoro-B-alanine, carbon dioxide and ammonium. Some authors[3] suggested that fluoroacetate, an intermediate product of catabolism of 5FU, inhibits the Krebs acid cycle. This causes a decreased production of adenosine triphosphato (ATP) which is necessary for the ATP-dependent urea cycle. When this happens, high levels of ammonia are incorporated into glutamine by glutamine synthetase. High Glutamine levels in cerebrospinal fluid have been reported in cases of chemotherapy-induced HE. This suggests an increased glutamine synthetasa activity which occurs primarily in astrocytes and may explain histopathological findings of astrocytosis and Alzheimer glia type II. High glutamine levels in astrocytes raise intracellular osmolality and result in astrocyte swelling and cerebral edema. Some authors have reported that

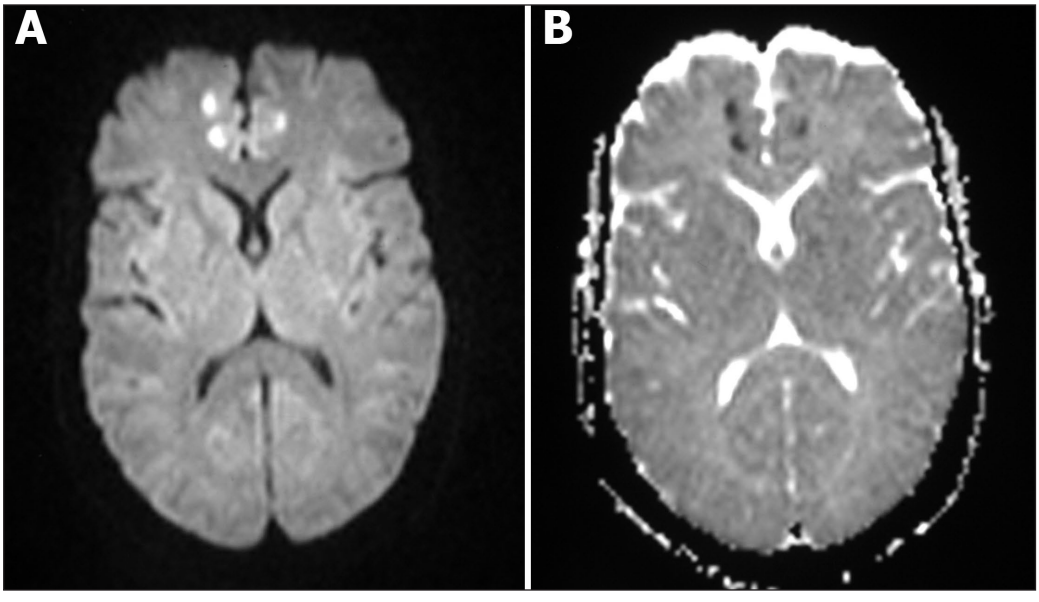

Figure 1: *Diffusion-Weighted Imaging (DWI) and Apparent Diffusion Coefficient (ADC) revealed restricted diffusion in the bilateral cingulate cortex.*

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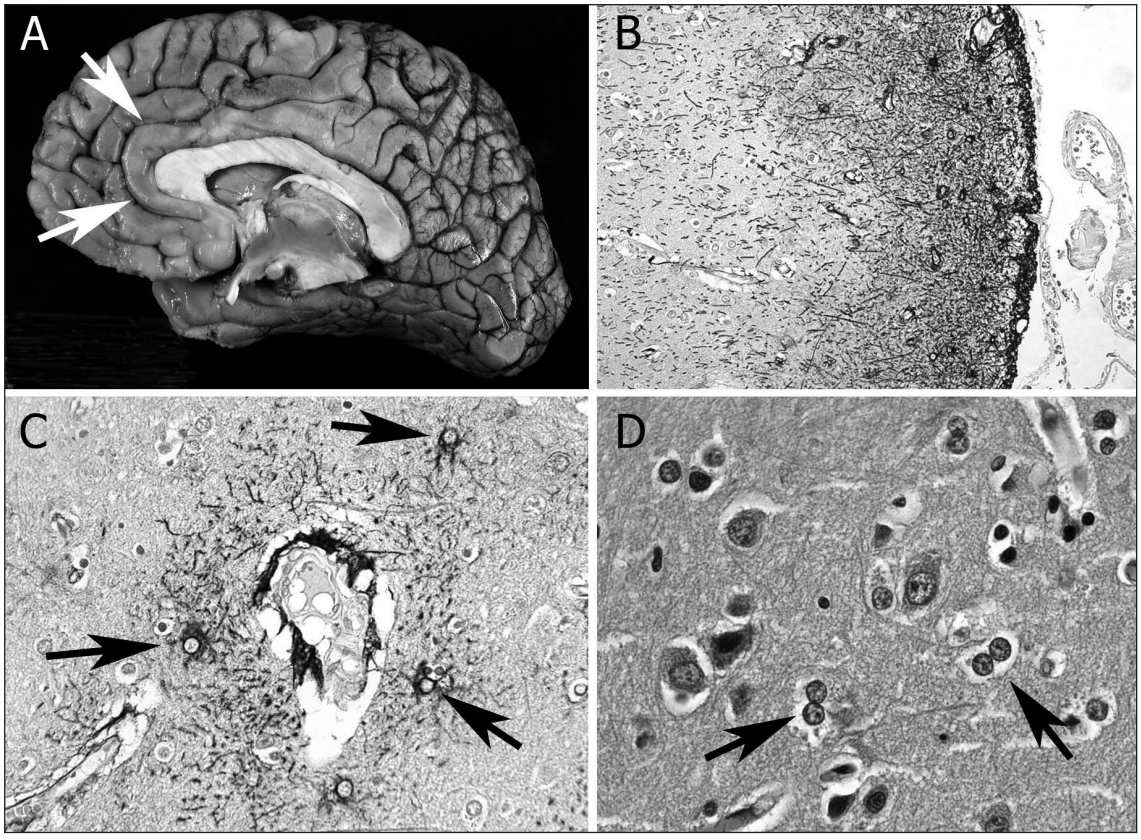

Figure 2: *In postmortem study, brain showed edema of the cingulate gyri (A) and temporal lobes. Histopathological findings revealed subpial (B) and perivascular (C) astrocytosis assessed by Glial Fibrillary Acidic Protein (GFAP) staining and Alzheimer type II glia assessed by Hematoxylin and Eosin (HE) staining (D).*

genetic polymorphisms of the thymidylate synthetase gene could contribute to the 5FU induced HE[4]. Moreover, as late-onset urea cycle deficiencies have been diagnosed in adults under stress situations or metabolic insults, a genetic mutation of these enzymes should be considered. Furthermore, some authors[1] found that only few patients receiving 5FU developed HE so concomitant factors such as infection, renal failure and dehydration should be considered.

Brain MRI should be performed to exclude structural etiologies. Cortical involvement of the cingulate gyri, temporal lobes and insular cortex has been typically described[5] in these cases.

In conclusion, if HE is suspected in patients receiving cytotoxics, brain MRI, liver and renal function tests should be required to exclude other etiologies. Amino acid tests should be considered to exclude partial urea cycle deficiencies.

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