5-Fluorouracil (5-FU) Induced Acute Toxic Leukoencephalopathy

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Case

This is a 57-year-old right-handed male with a history of locally advanced esophageal adenocarcinoma, who presented with confusion and speech changes. Patient received 5-Fluorouracil (5-FU) and cisplatin four days prior to presentation, which was complicated by very poor oral intake on day 2 of therapy. On the day of presentation, he was confused and his speech was slurred. The remainder of the neurologic Review of Systems was negative.

Physical examination revealed disorientation to place and time. He was able to follow commands. He had paucity of speech. He could not perform serial 7s, follow motor sequencing, and could not recall any of three items. He had dysarthria. Remainder of the cranial nerve exam was normal. He had no motor or sensory deficit. He had bilateral ataxia with finger-nose-finger and heel-shin, worse on the left compared to the right. He was unstable on his feet, and had a wide based gait.

Laboratory investigations were pertinent for acute renal failure (serum creatinine 6.78 mg/dL), thrombocytopenia, and anemia. Infectious work-up was unrevealing. The initial Magnetic resonance imaging (MRI) of the brain revealed diffuse bilateral restricted diffusion in the periventricular white matter and splenium of the corpus callosum (Figure 1). There were no correlating abnormalities seen on the Fluid attenuated inversion recovery (FLAIR) images. The remainder of the cranial MRI was unremarkable.

The radiographic diagnosis was "Toxic Leukoencephalopathy," likely secondary to 5-FU administration. The patient's oncologist discontinued the treatment plan that included the 5-FU, and the patient improved significantly the following day with supportive care. Subsequently, specialized genetic testing revealed that the patient was heterozygous for a dihydropyrimidine dehydrogenase (DPYD) gene mutation. The DPYD gene encodes the dihydropyrimidine dehydrogenase (DPD) enzyme.

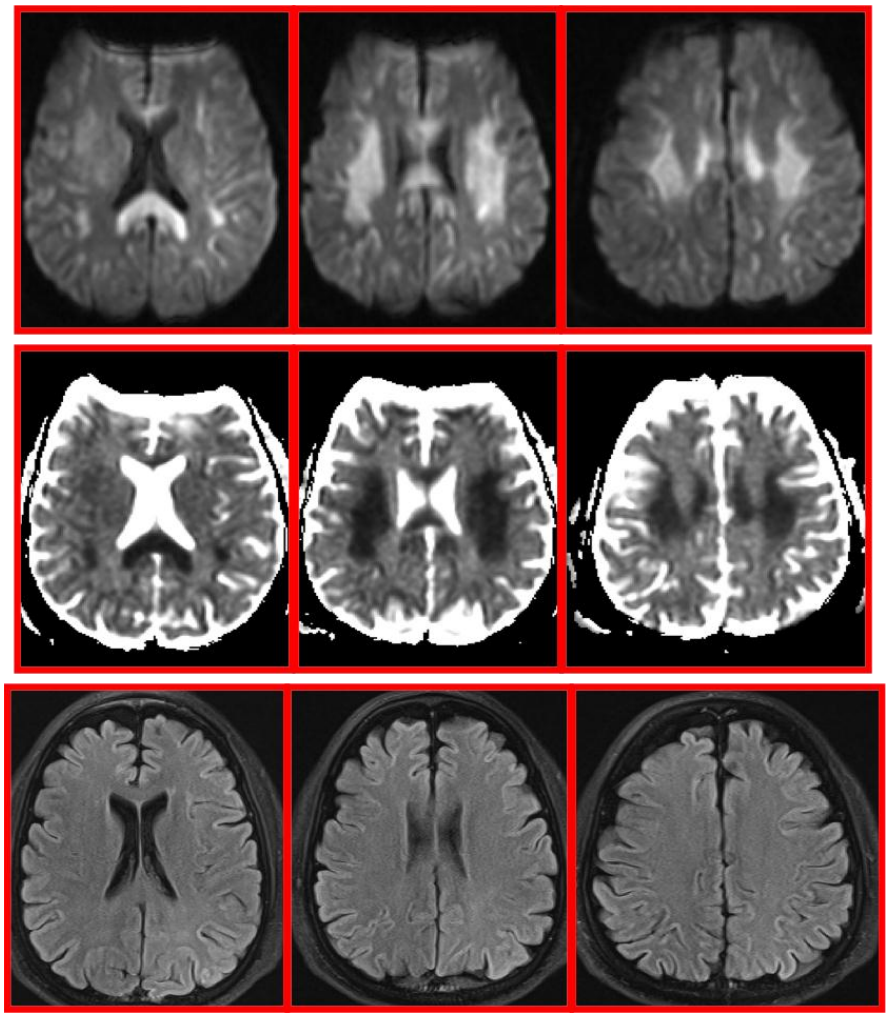

Figure 1: **Top row:** axial diffusion-weight imaging (DWI) demonstrating bilateral restricted diffusion in periventricular white matter and splenium of corpus callosum. **Mid row:** axial apparent diffusion coefficient (ADC) demonstrating hypointense signal correlating with DWI restriction. **Bottom row:** axial, fluid attenuated inversion recovery (FLAIR) images that do not any significant abnormality.

This mutation is associated with reduced DPD activity and increased risk for 5-FU sensitivity and toxicity. Therefore, the patient was diagnosed with an acute toxic leukoencephalopathy secondary to 5-FU administration in the setting of DPD deficiency. Repeat MRI of the brain two weeks later demonstrated persistent hyperintensity involving the splenium of the corpus callosum seen on axial FLAIR imaging (Figure 2). The acute DWI findings seen on the initial MRI were no longer present. Patient's clinical exam was practically normal except for ongoing bradyphrenia.

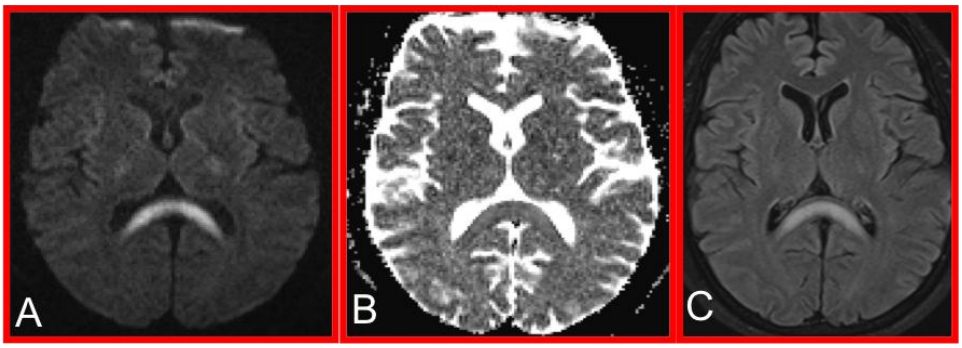

Figure 2: **A**: DWI, **B**: ADC, **C**: FLAIR. All three images are axial slices taken from the same level of the brain. The FLAIR imaging now demonstrates hyperintensity in the splenium of the corpus callosum. The hyperintensity seen in the DWI image likely represents T2 shine-through as there is no correlating hypointensity seen on the ADC sequence. The extensive bilateral periventricular restricted diffusion seen in Figure 1 has resolved

Discussion

The patient's presenting clinical picture was that of an encephalopathy, or diffuses cerebral dysfunction. The initial differential diagnosis is quite broad and includes systemic toxic-metabolic derangements (i.e. infection, electrolyte imbalance, ingestion, etc). The patient was in acute renal failure upon admission, which was likely contributing to his encephalopathy. However, the differential diagnosis must also include diffuse intrinsic brain pathologies like leukoencephalopathy, demyelination, CNS infection, embolic ischemic strokes, etc. For our patient, the MRI yielded the most useful information in determining the etiology. The neuroradiologist recognized the pattern of leukoencephalopathy as a known sequale of chemotherapy, and related it specifically to 5-FU.Nevertheless, it's unclear how much of the patient's encephalopathy was secondary to the leukoencephalopathy versus the acute renal failure. The patient had a normal serum creatinine prior to admission, and it quickly normalized in one to two days following intravenous hydration as did the patient's symptoms. Therefore, the acute renal failure was likely contributing to the encephalopathy, especially the apparent cortical dysfunction. It is, however, entirely plausible that the patient initially became encephalopathic from the toxic effects of 5-FU. It is, however, entirely plausible that the patient initially became encephalopathic from the toxic effects of 5-FU, which then led to poor oral fluid intake and acute renal failure. As the renal failure worsened, the patient's leukoencephalopathy may have become more symptomatic, creating a vicious cycle. There is a published case report of a similar patient who presented with acute confusion following 5-FU administration and almost identical

findings on brain MRI. The authors concluded that the patient's acute confusion was most likely secondary to the toxic leukoencephalopathy seen on MRI as induced by 5-FU. [1]

Unfortunately, the incidence of asymptomatic toxic leukoencephaloapthy is unknown, however, there is a considerable amount of evidence in the literature that patient's with DPD enzyme dysfunction/deficiency are at an increased risk for 5-FU toxicity.[2-4] 5-FU is a widely used fluorinated pyrimidine analogue chemotherapeutic agent that is used for the treatment of solid cancers such as carcinoma of the esophagus, stomach, intestines, and head and neck. 5-FU has two anti-neoplastic mechanisms; it interrupts DNA synthesis by decreasing the availability of thymidine, an essential DNA nucleoside, and it causes DNA strand breaks and cell death by the misincorporation of 5-FU metabolites into DNA and RNA.[5, 6] DPD enzyme is the rate limiting step in pyrimidine catabolism, and is responsible for the irreversible conversion of >85% of administered 5-FU into its inactive metabolite. The DPYD gene is located on chromosome region 1p22, and there are >30 polymorphisms. It is estimated that 3-14% of the population is at risk for 5-FU toxicity because of dysfunctional or deficient DPD enzyme activity. [3] DPD deficiency is diagnosed by commercial testing that uses polymerase chain reaction and detection primer extension to locate genetic mutations.

Approximately two million patients receive 5-FU worldwide each year, and up to 5-6% will experience neurotoxicity.[1, 7] The symptoms and signs of neurotoxicity include dizziness, weakness, numbness, ataxia, disorientation, confusion, agitation, seizure, coma, and death. The incidence of acute toxic leukoencephalopathy is unknown. By definition, toxic leukoencephalopathy implies a structural alteration of cerebral white matter in the presence of a toxin. [8] Animal and *in vitro* studies suggest that 5-FU leads to segmental vacuolation and swelling of myelin in the presence of 5-FU metabolites. [9] Histological examination reveals white matter pallor, vacuolation, axonal swelling with spheroids, oligodendrogilal swelling, enlarged spaces in or between myelin sheaths, diffuse macrophage infiltration with or without necrosis. The compartmentalization of water molecules within the vacuoles likely explains the restricted diffuse changes seen on DWI.

The prognosis of 5-FU acute toxic leukoencephalopathy is unclear, but there is evidence that it has some degree of reversibility.[1, 9] However, this may not always be the case, especially when white matter necrosis occurs and persistent MRI changes are seen. Previous efforts to predict clinical and radiographic reversibility have been inconclusive. [9] Therefore, it is very important to recognize this toxicity early so that the 5-FU can be discontinued and avoided. [9]

Teaching Points

- 5-FU can lead to neurotoxicity presenting as encephalopathy.
- Patients receiving 5-FU who develop encephalopathy should get an MRI, and DPD deficiency should be considered.
- DPD deficiency is now easily diagnosed with commercial genetic testing.
- 5-FU induced acute toxic leukoencephalopathy should be recognized early to avoid complications such as coma and death.

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