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Case Report

# 5-Fluorouracil-induced acute leukoencephalopathy: Case report and literature review ☆

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ABSTRACT

Toxic leukoencephalopathy (TL) refers to damage to the brain white matter following exposure to toxic agents. Multiple agents are incriminated in this condition, including chemotherapy drugs. 5-Fluorouracil, widely used in oncology, is responsible for neurotoxicity in less than 5% of cases. We report the case of a 54-year-old male patient who presented with neurological symptoms following 5-FU-based chemotherapy for gastric adenocarcinoma, and whose MRI scan revealed signs suggestive of toxic leukoencephalopathy. We also report on the evolution of the abnormalities described on his MRI after 1 year.



## Introduction

Toxic leukoencephalopathy is a disorder of the central nervous system of variable etiology affecting the white matter. Multiple agents are incriminated in this condition, including chemotherapy drugs. 5-Fluorouracil (5-FU) is widely used in digestive oncology as a part of many different chemotherapy protocols. 5-FU neurotoxicity is not common, but has been described in several cases as an acute or delayed adverse effect. 5-FU-induced acute toxic leukoencephalopathy may be reversible and must be recognized through MRI signs that are evocative in a patient who presents headaches, dysarthria, cerebellar syndrome, seizure, oculomotor disorders and/ or coma, following 5-FU medication [1]. Through this case report, we would like to show one of the MRI aspects of 5FU-related neurotoxicity and to illustrate the evolution of its appearance after an interval of 1 year.

## Case presentation

A 54-year-old male patient diagnosed with adenocarcinoma of the stomach, who underwent chemotherapy, gastrectomy with lymph node dissection, followed by postoperative

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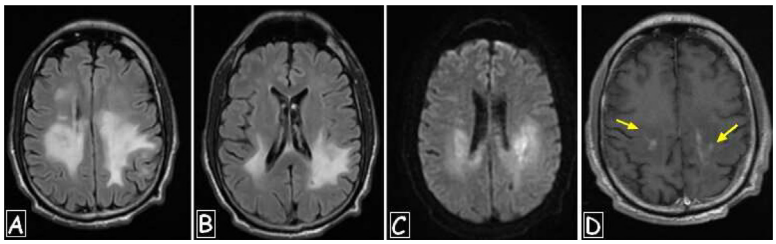


**Fig. 1 – Brain MRI showing FLAIR (A, B) and DWI (C) bilateral, symmetrical, and confluent hyperintensities of the periventricular white matter, with limited weak enhancement bilaterally (D).**

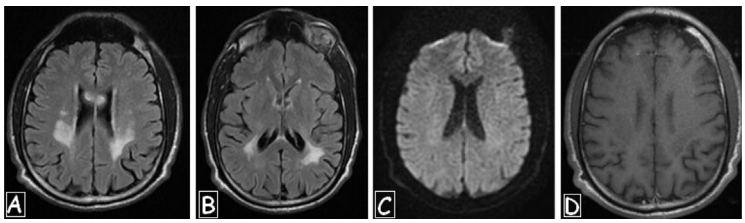


**Fig. 2 – Follow-up brain MRI 1 year later, showing the volume reduction of FLAIR hyperintensities (A and B), disappearance of the DWI hyperintensity (C) and contrast enhancement (D).**

chemotherapy. Immediately after the second session of adjuvant chemotherapy, the patient presented a behavioral disorder consisting of a sudden onset of agitation and stereotypic movements, with right lower limb weakness of 4/5. The chemotherapy protocol included an intravenous infusion of 5FU at a dose of 200 mg/m$^2$/24 h.

Laboratory tests showed no metabolic disorders with preserved renal and hepatic function. A Brain MRI was therefore performed, which revealed bilateral, symmetrical, confluent T2, FLAIR and DWI hyperintensities of the periventricular white matter, with limited weak enhancement bilaterally (Fig. 1). There was no sign of hemorrhage. The diagnosis of toxic leukoencephalopathy was made, the patient was put on corticosteroids and the 5-FU was stopped.

Clinical improvement was marked by the progressive disappearance of symptoms over a 2-month period. A follow-up MRI was performed 1 year later, which showed the volume reduction of T2 and FLAIR hyperintensities, disappearance of the DWI hyperintensity and contrast enhancement (Fig. 2).

## Discussion

Toxic leukoencephalopathy (TL) refers to damage to the brain white matter following exposure to toxic agents. 5-Fluorouracil, widely used in oncology, is responsible for neurotoxicity in less than 5% of cases. Female gender and hepatocellular insufficiency have been described as factors favoring the onset of TL [2]. This neurotoxicity is thought to be linked to ammonia accumulation in the blood as a result of inhibition of thymidylate synthetase in the Krebs's cycle following accumulation of fluoroacetate, which is a catabolic product of 5-FU [3]. Toxic leukoencephalopathy is revealed in more than 50% of cases within 48 hours after the first dose of 5-FU [4].

Several clinical signs of 5-FU neurotoxicity have been described, such as headache, dysarthria, cerebellar syndrome, oculomotor disorders, confusion, cognitive disorders, Parkinson's syndrome, seizure, and coma [5–7]. Diagnosis of TL is based on a number of arguments, including the onset of symptoms after taking 5-FU, and the exclusion of other etiologies that may explain the neurological signs [8].

The role of imaging in revealing the leukotoxic effect began to be studied in the 1980s among patients exposed to toluene [9]. CT scans are often normal, and MRI remains the gold standard for white matter exploration.

In toxic leukoencephalopathy, T2 and FLAIR diffuse hyperintensities of the deep periventricular white matter and corpus callosum are the most commonly described MRI signs. The basal ganglia, thalamus and U-fibers are generally unaffected. Abnormal contrast enhancement is a variable and inconstant finding [10]. These signs are suggestive of toxic leukoencephalopathy, as they reflect histological changes in the affected tissue, notably intramyelin and oligodendroglial edema (T2 and FLAIR hyperintensity), accumulation of vacuoles in myelin (DWI hyperintensity), and gadolinium enhancement could be explained by the blood-brain barrier (BBB) disruption due to the release of proinflammatory cytokines deleterious to the tight junctions of the BBB [2,10,11]. Perrain et al, in their series of 6 patients, reported no cases of gadolinium enhancement, which confirms the rarity of this sign and the atypical nature of our case [6]. DWI abnormalities are potentially reversible and can completely disappear [1].

Clinical and radiological signs may suggest other differential diagnoses, including metabolic or septic etiologies, uremic, or hypoxemic encephalopathy [8]. Posterior reversible encephalopathy syndrome (PRES) and acute toxic encephalopathy (ATL) may have similar clinical and even radiological signs, but on MRI, PRES has a cortical/subcortical distribution of abnormalities that is best seen on the FLAIR sequence, while ATL

tends to affect the periventricular white matter and is best analyzed on the DWI sequence [12].

Therapeutic management is mainly based on discontinuing the causative drug. Corticosteroids and antioxidants may be prescribed, as well as thiamine infusion and plasma exchange [2,10]. Uridine triacetate is a 5-FU antidote that can also be administered during the first 96 hours if available [5].

## Conclusion

Acute 5-Fluorouracil-induced leukoencephalopathy is one of the unusual aspects of the toxicity of this drug widely used in oncology. Its potentially reversible nature requires early diagnosis in order to stop the drug immediately. It's a diagnosis that radiologists need to be aware of, and which should be made in the presence of suggestive MRI abnormalities, taking into account the patient's context.

## Patient consent

An informed consent was obtained from the patient.

## Authors' contributions

All authors have made a significant contribution to this manuscript. All the authors have read and approved the final version of the manuscript.

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