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5-FU Induced Acute Toxic Leukoencephalopathy: Early Recognition and Reversibility on DWI-MRI

Shayan Sirat Maheen Anwar, Fatima Mubarak, Zafar Sajjad and Muhammad Azeemuddin

ABSTRACT

Acute toxic leukoencephalopathy (ATL) is a rare adverse effect of 5-Fluorouracil (5-FU) chemotherapeutic agent. It is imperative for the radiologist to confidently identify the white matter changes caused by this agent in case of toxicity. This will help in early detection and appropriate management of patient, as the condition is reversible both clinically and on imaging. We report a case of a 29 years old gentleman, known case of carcinoma of esophagus who suffered from acute toxic leukoencephalopathy secondary to leukotoxic therapeutic agent 5-FU, and illustrate the reversible imaging findings of this condition on withdrawal of the inciting agent.

Key Words: 5-FU. Diffusion weighted imaging (DWI). MRI. Toxic leukoencephalopathy.

INTRODUCTION

Toxic leukoencephalopathy is a progressive structural damage of white matter tracts involved in higher mental function. It is also known as toxic spongiform leukoencephalopathy.¹ Clinically, it is known to be reversible on withdrawal of toxic agent. Reversibility of imaging findings have been described in correlation with clinical improvement and categorically referred to as 'acute toxic leukoencephalopathy'.² Diffusion Weighted Imaging-Magnetic Resonance Imaging (MRI - DWI) play a pivotal role in picking up the abnormality in acute and sub-acute phase.

We describe this drug induced complication in a young patient with esophageal malignancy being treated with 5-FU.

CASE REPORT

A 29 years old young male, with advanced carcinoma of esophagus, was admitted for chemotherapy as consolidated treatment. On day 4th of 5-FU infusion, the patient developed discomfort and shortness of breath. ECG showed ventricular tachycardia run and rush call was generated. Loading dose of 1500 mg Magnesium was given intravenously (I/V) over 15 minutes with infusion rate of 125 mg/kg/hour. Calcium gluconate 1000 mg I/V stat was also injected. This reverted the rhythm to sinus rhythm. In view of 5-FU induced coronary spasm patient had non-ST elevation myocardial infarction and echocardiography showed ejection

fraction of 15 - 20%. Due to severe left ventricular systolic dysfunction, patient also suffered from acute kidney injury as his serum creatinine level rose from 0.9 mg/dl to 1.7 mg/dl and the creatinine clearance level was 49 ml/minute. He was, therefore, put on diuretics. Within 24 hours, the patient developed aphasia and right hemianopia with no motor weakness. EEG showed mild theta wave slowing of encephalopathy. MRI revealed bilateral symmetrical periventricular and deep white matter signal changes with diffusion restriction (Figure 1a), in keeping with acute toxic leukoencephalopathy.

His remaining chemotherapy was withheld and was given I/V methylprednisolone and levetiracetum. Patient responded well to this treatment and recovered completely from neurological symptoms in 2 - 3 days. His creatinine levels also normalized to 1.2 mg/dl from

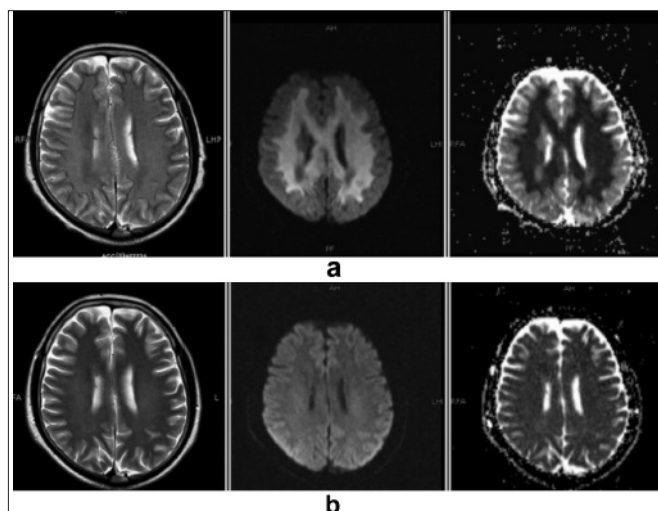


Figure 1: (a) Initial Brain magnetic resonance imaging (MRI) with symptoms. left image: T2-weighted MRI bilaterally symmetrical subtle hyper intensity in deep white matter of cerebral hemispheres, and corpus callosum. Middle and right image: DWI (b=1000) + ADC: Symmetrical high signal intensity in corresponding anatomical location with signal drop out on ADC. **(b)** Follow-up MRI with no symptoms: Complete resolution of deep white matter abnormal signals.

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maximum of 2.5 mg/dl. His hospital stay was about 10 days and he was discharged in stable condition.

Repeat MRI performed after 37 days of the initial scan revealed almost complete resolution of the DWI hyperintense signals in periventricular deep white matter with residual hyperintensity in splenium of corpus callosum (Figure 1b).

DISCUSSION

Toxic leukoencephalopathy typically presents with wide range of neurobehavioural symptoms including seizures, coma and death. It appears as diffuse bilateral symmetrical areas of diffusion restriction in periventricular and deep white matter and corpus callosum. There is sparing of cortex and subcortical white matter as well as basal ganglia.³ Exposure to variable extrinsic agents, like chemotherapeutic agents, cranial irradiation, narcotics, and environmental toxins lead to this condition.

In this patient, the cause of toxic leukoencephalopathy was induction therapy by 5-FU, which was reversible on withdrawal of drug and the imaging findings on DWI-MRI also showed reversibility on follow-up scan. Similar cases have been reported in the literature.^{3,4} McKinney *et al.* emphasized on the clinical and radiological correlation and reversibility of acute toxic leukoencephalopathy.²

Several chemotherapeutic drugs are responsible to induce leukoencephalopathy including methotrexate, vincristine, ifosfamide, fludarabine, cytarabine, 5-fluorouracil, cisplatin and the interferons. Among them, 5-FU has been frequently reported as a causative agent of leukoencephalopathy. However, the reported incidence is less than 5% and the cause is multifactorial.⁵

5-FU readily penetrates the blood brain barrier and is a fluorine-substituted analogue of pyrimidine uracil, which blocks DNA synthesis. Dihydropyrimidine dehydrogenase (DPD) deficiency is a risk factor for 5-FU-induced leukoencephalopathy as it is responsible for major catabolism of this drug *in vivo*. The exact pathophysiology of drug induced leukoencephalopathy is unknown. Past studies *in vitro* and *in vivo* has postulated that in acute phase there is myelin destruction, vacuolization; myelin swelling and macrophage infiltration resulting in restricted movement of free water. This explains the high intensity signals in DWI-MRI secondary to this cytotoxic oedema.⁶

The imaging mimickers of ATL are posterior reversible encephalopathy syndrome (PRES) and radiation induced angiopathy. PRES can be induced by similar drugs and chemotherapeutic agents, such as cyclosporin, tacrolimus, and interferon alfa.⁷ Posterior reversible encephalopathy typically involves cortex and subcortical white matter on FLAIR in early phase and

subsequently involves periventricular white matter in severe cases. Diffusion restriction occurs in minority of cases.

On the other hand, in radiation injury, there is small vessel ischaemic demyelination which in acute phase, returns hyper intense signals on FLAIR in periventricular deep white matter which is asymmetrical and lacks diffusion restriction.⁸

Other close differentials of ATL includes carbon monoxide poisoning and inhaled opiates, They are also potentially reversible and show diffusion restriction in acute phases, however, have subtle variations on imaging, therefore, clinical history plays a pivotal role. Acute carbon monoxide poisoning affects deep white matter in early stages with diffusion restriction and later involves the deep gray matter, which is a reversible finding.⁹ Heroin induced leukoencephalopathy typically shows symmetric subcortical and periventricular white matter hyperintensity on diffusion weighted images, specifically involving the cerebral and cerebellar white matter and deep gray matter.¹⁰

In conclusion, it is imperative for the radiologist to rightly identify the distribution and pattern of the abnormality to give a prompt diagnosis and alert and expedite the withdrawal of causative agent. The role of primary physician in providing appropriate clinical history cannot be denied in the same instance, as many of the toxic agents have overlapping imaging features.

REFERENCES

1. Filley CM, Kleinschmidt-DeMasters BK. Toxic leukoencephalopathy. *N Engl J Med* 2001; **345**:425-32.
2. McKinney AM, Kieffer SA, Paylor RT, Santa Cruz KS, Kendi A, Lucato L. Acute toxic leukoencephalopathy: potential for reversibility clinically and on MRI with diffusion-weighted and FLAIR imaging. *AJR Am J Roentgenol* 2009; **193**:192-206.
3. Akitake R, Miyamoto S, Nakamura F, Horimatsu T, Ezoe Y, Muto M, *et al.* Early detection of 5-FU-induced acute leukoencephalopathy on diffusion-weighted MRI. *Jpn J Clin Oncol* 2011; **41**:121-4.
4. Sivasubramanian S, Moorthy S, Sreekumar K, Kannan RR. Diffusion-weighted magnetic resonance imaging in acute reversible toxic leukoencephalopathy: a report of two cases. *Indian J Radiol Imaging* 2010; **20**:192-4.
5. Yeh KH, Cheng AL. High-dose 5-fluorouracil infusional therapy is associated with hyperammonaemia, lactic acidosis and encephalopathy. *Br J Cancer* 1997; **75**:464-5.
6. Tha KK, Terae S, Sugiura M, Nishioka T, Oka M, Kudoh K, *et al.* Diffusion weighted magnetic resonance imaging in early stage of 5-fluorouracil-induced leukoencephalopathy. *Acta Neurol Scand* 2002; **106**:379-86.
7. McKinney AM, Short J, Truwit CL, McKinney ZJ, Kozak OS, SantaCruz KS, *et al.* Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. *AJR* 2007; **189**:904-12.

8. Welzel T, Niethammer A, Mende U, Heiland S, Wenz F, Debus J, *et al.* Diffusion tensor imaging screening of radiation-induced changes in the white matter after prophylactic cranial irradiation of patients with small cell lung cancer: first results of a prospective study. *AJNR* 2008; **29**:379-83.
9. Sener RN. Acute carbon monoxide poisoning: diffusion MR imaging findings. *AJNR Am J Neuroradiol* 2003; **24**:1475-7.
10. Bega DS, McDaniel LM, Jhaveri MD, Lee VH. Diffusion weighted imaging in heroin-associated spongiform leukoencephalopathy. *Neurocrit Care* 2009; **10**:352-4.

