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LETTER TO THE EDITOR

Acute leukoencephalopathy and thyroiditis induced by capecitabine

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To the Editor,

Capecitabine is an oral fluoropyrimidine antimetabolite drug commonly used in several cancer types. Neurological toxicity rarely occurs. We report a case of acute capecitabine-induced leukoencephalopathy and thyroiditis in a breast cancer patient, both rapidly regressing after treatment discontinuation. We discuss hypotheses regarding the physiopathology of these toxic side effects.

A 42-year-old female without past medical history was diagnosed in 2019 with early triple negative ductal breast carcinoma, treated with neoadjuvant chemotherapy (epirubicin–cyclophosphamide followed by paclitaxel), surgery and adjuvant radiotherapy. Axillar nodal recurrence was observed in February 2021 and treated by node excision. Adjuvant treatment with capecitabine was started (1500 mg bid 2 weeks out of three) after excluding dihydropyrimidine dehyrogenase (DPD) deficiency (uracilemia 9.2 ng/ml, normal range < 14.0 ng/ml). After 3 days of treatment, the patient developed progressively worsening faintness, dysarthria, postural instability and headache, without any non-neurological complaint. Neurological examination in the emergency department only revealed lowered speech. Viral serologies and auto-immune assays were negative. Gadolinium-enhanced brain MRI revealed bilateral and symmetric hyperintense lesions within the corpus callosum, the supratentorial white matter and the corticospinal tracts on diffusion and T2/FLAIR (fluid-attenuated inversion recovery) weightings (Fig. 1a–c). Cerebrospinal fluid analysis was normal (negative multiplex PCR and cytologic examination, no oligoclonal bands or auto-antibodies). Capecitabine was interrupted at hospital admission and symptoms gradually disappeared, with full recovery after 10 days and almost MRI normalization 5 months later (Fig. 1d–f).

Acute hypothyroidism due to a Hashimoto thyroiditis was discovered at admission (TSH level of 78 mU/l (normal range 0.27–4.2), free T4 of 10.3 pmol/l (normal range 12.0–22.0) and positive anti-TPO antibodies). No L-thyroxine substitution was initiated. The hypothyroidism spontaneously improved with control TSH levels at 16.23 mU/l and T4 level normalization 1 month later. Thyroid ultrasonography was normal.

Capecitabine is an oral fluoropyrimidine antimetabolite, converted by thymidine phosphorylase to 5-fluoro-uracil (5-FU), an analogue of uracil. Several of its metabolites interfere with nucleoside metabolism and DNA/RNA synthesis, resulting in cell cycle arrest and cell death. The main side effects of these drugs include fatigue, diarrhea, mucositis, hematological toxicity and palmo-plantar erythrodysesthesia. Central nervous system toxicity is rare and includes cerebellar toxicity, encephalopathy and peripheral neuropathy. The diagnosis of acute capecitabine-induced leukoencephalopathy is based on the chronology of the medication uptake and MRI features. Nausea, vertigo, headache, confusion, coma, ataxia, diplopia, paresthesia, dysgraphia and dysarthria have been described, usually occurring within the first days of treatment.

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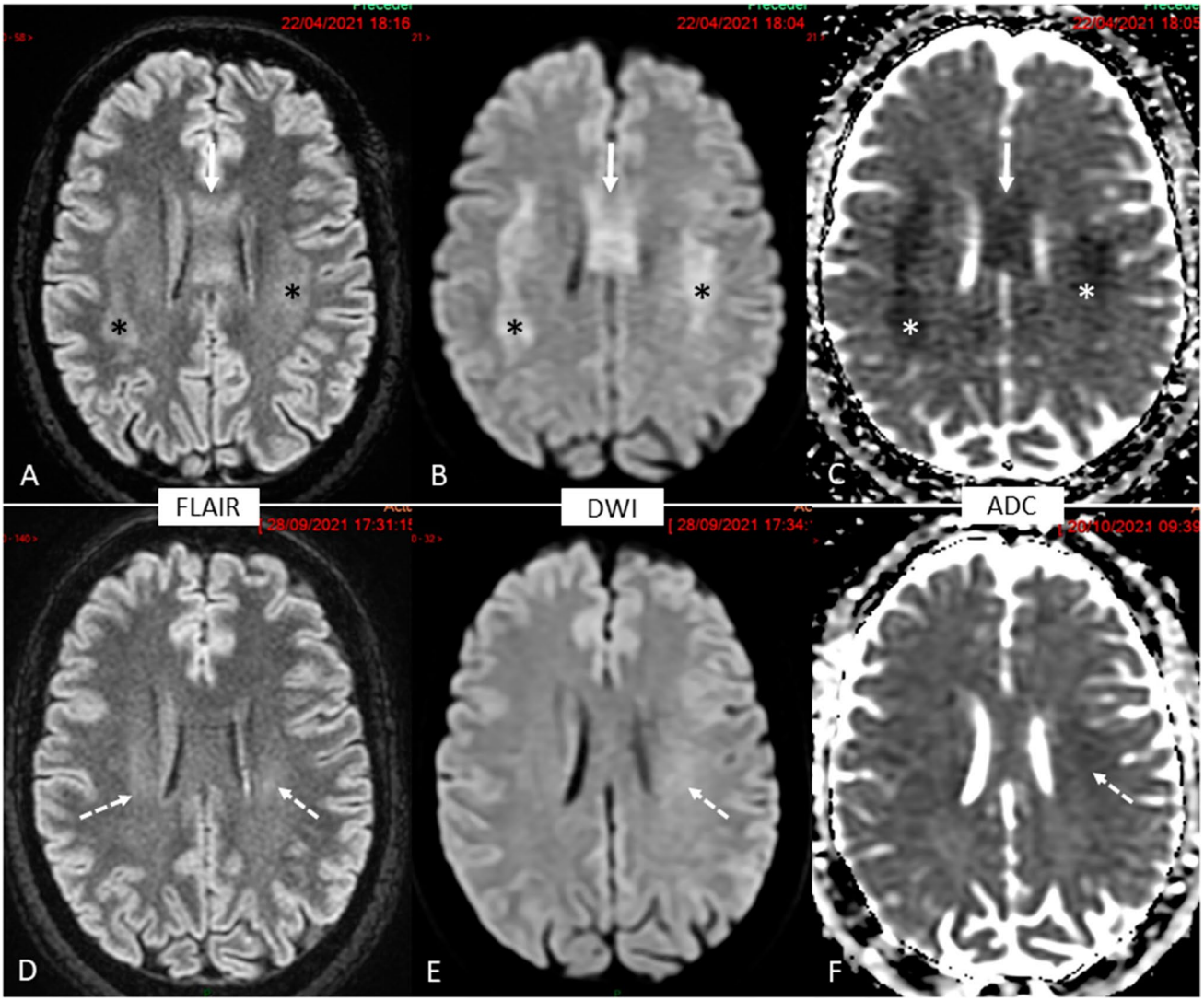

Fig. 1 MRI work-up: **a**–**c** initial MRI at presentation. **d**–**f** Follow-up examination 5 months later. All views show similar axial-transverse slice location through the corpus callosum. **a** FLAIR (fluid-attenuated inversion recovery) view showing an increased signal intensity within the corpus callosum (arrow) and the hemispheric white matter (asterisks). **b** Diffusion-weighted (DWI) view showing abnormally increased signal intensity within diseased areas. **c** Apparent diffusion coefficient (ADC)-mapped image revealing low ADC values reflecting restriction of water diffusivity pathognomonic for cytotoxic edema within diseased areas. **d**–**f** Corresponding views to previous illustrations 5 months later showing complete subsidence of signal abnormalities within the corpus callosum, and almost complete subsidence of those within the hemispheric white matter with only subtle residual abnormalities (stripped arrows) corresponding to slight gliotic scaring

If not performed before, DPD deficiency should be excluded, especially if mucositis, diarrhea or bone-marrow suppression co-occurs. Brain MRI can confirm cytotoxic capecitabine-induced leukoencephalopathy by revealing reversible bilateral and symmetric lesions of the supra-tentorial deep white matter, corpus callosum and corticospinal tract. Damaged brain areas display high signal intensity on both T2/FLAIR and diffusion-weighted (DW) views with decreased apparent diffusion coefficient (ADC) within lesions featuring cytotoxic edema [1]. Posterior reversible encephalopathy syndrome (PRES) is another neurological complication of capecitabine, of later onset, inducing headache, seizures, loss of vision, mental state alteration and associated with significant hypertension. MRI allows its differentiation from toxic leukoencephalopathy as PRES lesions are vasogenic edema displaying low signal intensity on DW images with elevated ADC values contrary to cytotoxic edema, even if abnormally elevated T2/FLAIR signal intensity of the lesions is similarly observed in both conditions. Tissue damage in PRES may be observed in all brain areas, but prominently in the posterior areas of the parietal, temporal and occipital lobes [2].

Acute capecitabine-induced leukoencephalopathy could be due to the direct toxicity of the drug or its metabolites. 5′-Deoxy-5-fluorouridine, an intermediate metabolite of capecitabine, is able to cross the blood–brain barrier, whereas capecitabine might also have a toxic effect on its endothelium. Thymidine phosphorylase is, furthermore, preferentially expressed in the cerebral white matter cells, where 5-FU, therefore, could accumulate [3]. Indirect toxic effects of the drug on the cell metabolism could also play a role: in vitro studies suggest that 5-FU can lead to thiamine deficiency through the inhibition of its phosphorylation. Moreover, fluoroacetate, another 5-FU metabolite, leads to the intracellular accumulation of ammonia, inhibiting the Krebs cycle [2].

The symptoms are usually reversible within the first days after drug withdrawal. Administration of steroids and thiamine has not proven to reverse toxicity. Uridine triacetate is a pyrimidine analogue able to reverse early onset severe 5-FU or capecitabine toxicities by competing with the toxic 5-FU metabolite fluorouridine triphosphate [4]. A case report suggested that rechallenging at lower doses could be an option when the benefit overweights the risk if no alternative treatment is available [5]. Nevertheless, given the probable pathophysiology of the toxicity, reintroduction should be avoided.

Observational studies suggested a correlation between fluoropyrimidine treatment and hypothyroidism. Structural similarities between 5-FU and propylthiouracil, a thioamide drug that inhibits thyroperoxidase, necessary for the production of T4 and T3 could explain the phenomenon [6]. Our patient had normal thyroid hormone levels at breast cancer diagnosis, but these were not controlled before capecitabine administration. She could have been suffering from thyroiditis at baseline, subsequently unable to raise her production of thyroid hormones during treatment.

This case report emphasizes the importance of recognizing capecitabine-related leukoencephalopathy, as drug discontinuation results in a rapid clinical and radiological improvement. Capecitabine may also affect the metabolism of thyroid hormones.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical statement and Informed consent The ethics committee of Cliniques universitaires Saint-Luc approved the study. Informed consent was obtained from the patient. All the procedures performed were part of the routine care.

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