CASO CLÍNICO/CASE REPORT

RESLES: 5-Fluorouracil Encephalopathy

RESLES: Encefalopatia por 5-Fluorouracil

Correia RR[1,*]; Vieira PL[2]; Paiva P[2]; Martin S[2]; André ME[2]

1-https://orcid.org/0000-0002-7948-7346 / Mestrado / Centro de Responsabilidade Integrado de Medicina Interna / ULS Castelo Branco, Castelo Branco, Portugal.

2-Mestrado / Centro de Responsabilidade Integrado de Medicina Interna / ULS Castelo Branco, Castelo Branco, Portugal.

Informações/Informations:
Caso Clínico, publicado em Sinapse, Volume 20, Número 1, janeiro-março 2020. Versão eletrónica em www.sinapse.pt
Case Report, published in Sinapse, Volume 20, Number 1, january-march *2020. Electronic version in www.sinapse.pt*

Keywords:
Corpus Callosum;
Encephalitis;
Fluorouracil / adverse effects;
Neurotoxicity Syndromes;
Nervous System Diseases / chemically induced.

Palavras-chave:
Corpo Caloso;
Doenças do Sistema Nervoso/ induzido quimicamente;
Encefalite;
Fluorouracil /efeitos adversos;
Síndromes Neurotóxicas.

***Autor Correspondente / Corresponding Author:**
Rita Reis Correia
Rua Dr. António Trindade
6000-351 Castelo Branco,
Portugal
rt_correia@hotmail.com

Recebido / Received: *2020-01-20*
Aceite / Accepted: *2020-04-19*
Publicado / Published: *2020-06-30*

DOI: 10.46531/sinapse/CC/200003/2020

Abstract

A 54-year-old man undergoing palliative chemotherapy for pancreatic adenocarcinoma with 5-fluorouracil resorted to the emergency department for progressive drowsiness, disorientation and decreased visual acuity, 24 hours after chemotherapy. He presented posterior aphasia and a right hemiparesis (grade 4 with preserved face). Magnetic resonance imaging showed a high signal intensity lesion in the centrum of the splenium of the corpus callosum in T2 weighted, a hypointensity in the T1 and a restriction in the DWI. A diagnosis of ammonia encephalopathy secondary to 5-fluorouracil was made. Treatment was started with thiamine and lactulose. Despite a slight symptomatic improvement, the patient died a month later due to the evolution of the underlying cancer.

Resumo

Homem de 54 anos sob quimioterapia paliativa com 5-fluorouracil para um adenocarcinoma pancreático, recorreu ao Serviço de Urgência por prostração progressiva, desorientação e diminuição da acuidade visual, 24 horas após sessão de quimioterapia. Ao exame objectivo, apresentava afasia posterior e hemiparesia direita (grau 4 com face preservada). A ressonância magnética mostrou uma lesão de alta intensidade de sinal no centro do esplênio do corpo caloso em T2 ponderada, baixa intensidade em T1 e restrição em DWI. Assumiu-se o diagnóstico de encefalopatia por amónia secundária ao 5-fluorouracil. O tratamento foi iniciado com tiamina e lactulose. Apesar de uma ligeira melhoria sintomática, o paciente morreu um mês depois devido à evolução subjacente do carcinoma.

Introduction

Neurotoxicity is an important cause of neurological disorders, and should be excluded in patients with abnormal neurological examination.[1] RESLES is a reversible splenial lesion syndrome.[2] Several causes are described in the literature, including chemotherapy.[1]

Neurotoxicity induced by 5-fluorouracil (5-FU) is rare and usually reversible, especially if the diagnosis is early and the drug is discontinued.[3,4] The clinical presentation is nonspecific, but neuroimaging is usually characteristic.[1] We report a case that reflects the importance of this approach.

Case Report

A 54-year-old Caucasian man present with 48 hours of progressive history of drowsiness, disorientation and decreased visual acuity. Two months before, he was diagnosed with pancreatic adenocarcinoma, with hepatic metastasis. He was undergoing palliative chemotherapy with the DeGramont protocol (folinic acid-200 mg/m2; 5-FU-400 mg/m2). His medical and family history was unremarkable for other conditions. Twenty-four hours after the completion of the first cycle of chemotherapy, the patient was admitted at the emergency room with the referred symptoms. The patient was normotensive, euglycemic and afebrile.

Neurological examination revealed mild apathy, trouble obeying commands, disorientation for time and place and impaired attention (difficult to perform forward and backward digit span test). Cranial nerves examination was normal. Muscle strength was normal, except for grade 4-5 in right upper extremity.

Serum analysis showed elevated alkaline phosphatase (725 U/L; normal range, 38-126 U/L) and ammonia (36 μmol/L; normal range 9-30 μmol/L). A respiratory alkalosis with hypocapnia was present in the blood gas analysis. Biochemistry and culture of cerebrospinal fluid were normal. No abnormal findings were detected in brain computer tomography (CT) images. Magnetic resonance imaging in T2 weighted showed a hypersignal lesion in the centrum of the splenium of the corpus callosum (**Fig.s 1B e C**), a hypointensity in T1 (**Fig.1A**) and with restriction diffusion on DWI (**Fig.1D**) After exclusion of infectious, vascular, auto-immune and neoplastic etiologies, it was assumed the diagnosis of ammonia encephalopathy secondary to 5-FU.

Treatment with thiamine and lactulose was initiated.

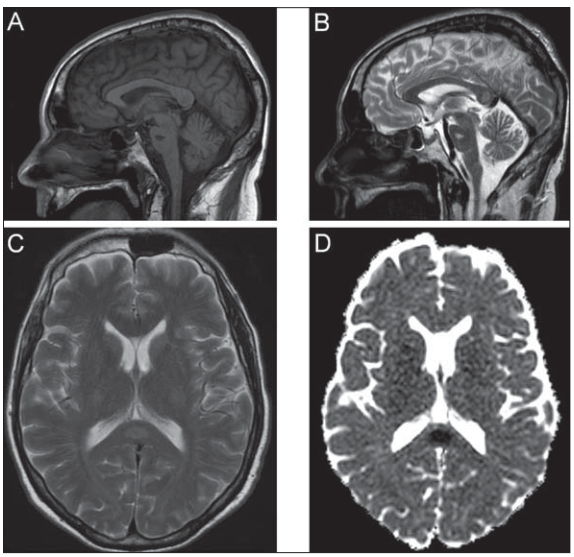

Figure 1. Magnetic resonance imaging in T2 weighted showed a hypersignal lesion in the centrum of the splenium of the corpus callosum (Fig.1B e C), a hypointensity in T1 (Fig.1A) and with restriction diffusion on DWI (Fig.1D)

Despite a slight symptomatic improvement, the patient died a month later due to the evolution of the underlying cancer.

Discussion

5-FU is a fluorine-substituted analogue to pyrimidine uracil, whose main action is to block DNA synthesis by inhibition of the thymidylate synthetase. The catabolism of pyridine is performed in 85% of the cases by the dihydropyrimidine dehydrogenase (DPD).[4,5]

5-FU induced neurotoxicity is uncommon. The acute form often consists of an encephalopathy and symptomatology may vary from confusion or ataxia to seizures.[3,5-7]

In the literature, the symptoms usually start on average 9 hours after administration and the complete recovery appears 15 hours after discontinuation.[6,7]

The exact pathological process associated to drug-induced leukoencephalopathy remains unclear.[4,7] There are two hypotheses accepted for explaining this process: the first one considers that the injury is caused by the ammonia increase. The 5-FU activity consists of blocking Krebs cycle by fluoroacetate, a product of fluorouracil catabolism, thus interfering with the urea cycle.[3,5,7-9] An alternative explanation is that the drug is capable of increase thiamine metabolism inducing a deficit of thiamine, similar to the Wernicke syndrome.[3,5,9] Apart from the pathological process, the final lesion consists of myelin destruction, even in the early stage of the disease.[4]

Several studies suggest that DPD deficiency may be a risk for 5-FU induced leukoencephalopathy.[3-6]

The predilection for the splenium of the corpus callosum is unclear, but may be associated to its relative lack of adrenergic innervation, making it susceptible to hypoxic vasodilatation and autoregulation failure with consequent overperfusion.[2]

Based on the literature, the diagnostic criteria include: (1) development of encephalopathy during or shortly after administration; (2) Exclusion of other metabolic or physical factors that may have an effect on the consciousness level, such as hyperglycemia, hypoglycemia, azotemia, hepatic failure, electrolyte imbalance, sepsis, central nervous system involvement of cancers or vascular causes; (3) exclusion of a drug effect caused by concomitant medications.[5,6]

Hyperammonemia, lactic acidosis and hypocapnia were often found concomitantly in the development of encephalopathy.[4,7,10]

Diffusion-weighted magnetic resonance imaging (DWI-MRI) is more sensitive than CT scan for white matter. For this reason, DWI-MRI is the best method to early detection of RESLES and allows the definitive diagnosis of this characteristic encephalopathy.[4,11]

The common presentation is a high signal intensity lesion in white matter and corpus callosum in T2 weighted MRI.[1,4,11]

In one study, electroencephalogram (EEG) examinations of eight patients revealed diffuse cortical dysfunction with diffuse slow waves or diffuse intermittent theta waves, suggesting metabolic or toxic encephalopathy.[5-7]

Our patient fulfilled all the criteria, which allowed the diagnosis. Like other described cases, the common symptoms started in the first week after chemotherapy, with increased ammonia and a characteristic image at MRI.

Diagnosis of posterior reversible encephalopathy sis less likely because it usually involves posterior subcortical white matter.[12]

The treatment consists of the discontinuation the 5-FU and the administration of thiamine and lactulose.[2,5,10] When necessary, corticosteroids and anticonvulsant have been administered.[1,5]

In summary, RESLES is a splenic-restricted lesion of the corpus callosum, usually clinically and radiologically reversible, with an excellent prognosis, except in patients with an underlying severe disorder such as ours.[2] ■

Acknowledgement / Agradecimento:

Doctor José Tomás (Serviço de Neurologia/ULS Castelo Branco, Castelo Branco, Portugal), was essential in the whole process of reviewing the case.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Consentimento: Consentimento do doente para publicação obtido.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Patient Consent: Consent for publication was obtained.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

References / Referências

1. Lucato LT, McKinney AM, Short J, Teksam M, Truwit CL. Reversible findings of restricted diffusion in 5-fluorouracil neurotoxicity. Australas Radiol. 2006;50:364-8.
2. Garcia-Monco JC, Cortina IE, Ferreira E, Martínez A, Ruiz L , Cabrera A, et al. Reversible splenial lesion syndrome (RESLES): what's in a name? J Neuroimaging. 2011;21:e1-14. doi: 10.1111/j.1552-6569.2008.00279.x.
3. Pellacani C, Eleftheriou G. Neurotoxicity of antineoplastic drugs: Mechanisms, susceptibility, and neuroprotective strategies. Adv Med Sci. 2020;65:265-85. doi: 10.1016/j.advms.2020.04.001.
4. R, Miyamoto S, Nakamura F, et al. Early detection of 5-FU-induced acute leukoencephalopathy on diffusion-weighted MRI. Jpn J Clin Oncol. 2011;41:121-4.
5. Pirzada NA, Ali, II, Dafer RM. Fluorouracil-induced neurotoxicity. Ann Pharmacother. 2000;34:35-8.
6. 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.
7. Mitani S, Kadowaki S, Komori A, Sugiyama K, Narita Y, Taniguchi H, et al. Acute hyperammonemic encephalopathy after fluoropyrimidine-based chemotherapy. Medicine. 2017;96:e6874. doi: 10.1097/MD.0000000000006874.
8. Marella H, Peravali R, Jain A, Nair S, Maliakkal B, Agbim U, et al. Hyperammonemic encephalopathy associated with 5-fluorouracil in a patient with previous orthotopic liver transplantation. Bay Univ Med Cent Proc. 2020;33:256-7. doi: 10.1080/08998280.2019.1708689
9. Cho IJ, Chang HJ, Lee KE, Won HS, Choi MY, Nam EM, et al. A case of Wernicke's encephalopathy following fluorouracil-based chemotherapy. J Korean Med Sci. 2009;24:747-50. doi: 10.3346/jkms.2009.24.4.747.
10. Cheung WY, Fralick RA, Cheng S. The confused cancer patient: a case of 5-fluorouracil-induced encephalopathy. Curr Oncol. 2008;15:234-6.
11. Xu W, Zhou Y, Jiang Y, Zhang L, Tang Q. Clinical and magnetic resonance imaging features of reversible splenial lesion syndrome in adults: a small case series. Eur Neurol. 2019; 82:86-92. doi: 10.1159/000505019.
12. Mehta S, Singh G, Paul BS. Teaching NeuroImages: 5-FU-induced acute leukoencephalopathy. Neurology. 2013;80:e191. doi: 10.1212/WNL.0b013e3182904d03.
13. Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. J Neurol. 2017;264:1608-16. doi: 10.1007/s00415-016-8377-8.
14. Elkiran ET, Altundag K, Beyazit Y, Guler N, Kars A. Fluorouracil-induced neurotoxicity presenting with generalized tonic-clonic seizure. Ann Pharmacother. 2004;38:2171. doi: 10.1345/aph.1E070