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Case Report

Hepatocellular adenomas associated with antiepileptic drugs: A case report ☆

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ARTICLE INFO

Article history:
Received 3 October 2024
Revised 29 December 2024
Accepted 3 January 2025

Keywords:
Hepatocellular adenoma
Rasmussen encephalitis
Antiepileptic drugs
HNF1 alpha-inactivated
Risk factor
Male

ABSTRACT

Hepatocellular adenoma (HCA) represents a rare benign liver tumor occurring predominantly in females of reproductive age and taking oral contraceptives. They are associated with various conditions. We report the case of a male patient with hepatic adenomas who has an association with long-term antiepileptic drugs in treatment for seizures of Rasmussen's encephalitis without a history of anabolic steroid use or any underlying hyperestrogenism. MRI findings show multiple hepatic nodules with mainly intermediate signal on T2, intratumoral fat content without diffusion restriction, and intense enhancement in the arterial phase with and without washout in portal and equilibrium phases. The imaging characteristics of these adenomas are indicative of the HNF1 alpha-inactivated subtype. No therapeutic interventions have been performed so far. This association is rare, and few cases have been reported in the literature. This case aims to reaffirm and remind people of the association of hepatic adenomas with antiepileptic drug use and make an additional analysis of the new molecular subtypes of hepatic adenoma, described recently in the literature. Exhaustive literature research reveals few case reports.

Introduction

Hepatocellular adenomas (HCAs) are rare benign neoplasms arising from hepatocytes, occurring at a rate of 3–4 per 100,000 [1]. Among men, the incidence is even lower [1]. Risk factors for the development of HCAs include oral contraceptives, androgen hormone imbalance, obesity, alcohol intake, antiepileptic drugs, liver vascular disease, chronic viral hepatitis, cirrhosis, previous malignancy, and germline genetic susceptibility [1–3]. To date, there are no reports in the South American population of hepatocellular adenoma associated with phenobarbital therapy. We describe 1 case concerning a young adult male with Rasmussen's encephalitis, an epileptogenic progressive disease, in long-term use of phenobarbital with hepatocellular adenoma associated.

Case

A 32-year-old man diagnosed with Rasmussen encephalitis, an epileptogenic syndrome, has had seizures since the age of

☆ Competing Interests: The authors have declared that no competing interests exist.

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https://doi.org/10.1016/j.radcr.2025.01.015

Table 1 Table – Values of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), direct bilirubin (DB), indirect bilirubin (IB), γ-glutamyltransferase (GGT), alkaline phosphatase (ALP), C-reactive protein (CRP) after surgery.

LAB	Level (jan, 05)	Level (nov, 06)	Level (dez, 17)
ALT	22 U/L	65 U/L	27 U/L
AST	25 U/L	26 U/L	20 U/L
TB	0,41 mg/dL	0,81 mg/dL	0,40 mg/dL
DB	0,20 mg/dL	0,40 mg/dL	0,20 mg/dL
IB	0,30 mg/dL	0,50 mg/dL	0,20 mg/dL
GGT	—	662 U/L	383 U/L
ALP	—	253 U/L	172 U/L
CRP	—	22,4 mg/L	2,9 mg/L

6 and has been on antiepileptic drugs since then. Seizures are currently preceded by dizziness and bright spots in the right visual hemifield, lasting 15 seconds, followed by extension of the upper and lower limbs and cephalic version to the left. No noteworthy family history was featured.

In October 2023, the patient was referred and admitted to our institution due to acute cholecystitis, with classic clinical symptoms of epigastric pain, choluria, and fecal acholia.

The physical examination indicated mild distress, with a positive Murphy's sign.

On neurological examination, the patient was alert but exhibited impaired sustained attention, sensory aphasia, and negative myoclonus in the upper right limb.

After surgery, the patient showed good progress and was discharged from the hospital. However, he continued to experience symptoms related to his underlying condition, which have progressively worsened and become challenging to manage.

To evaluate elevated liver enzymes and bilirubin levels following laparoscopic cholecystectomy, a computed tomography (CT) scan and magnetic resonance imaging (MRI) were performed, as shown in the table below (Table 1). Intraoperative findings revealed acute gangrenous cholecystitis with no signs of malignancy. Additionally, multiple hepatic adenomas were incidentally discovered.

The patient uses lamotrigine (daily dose of 300 mg) and clobazam (daily dose of 20 mg) as antiepileptic drugs and denies having used anabolic steroids.

Portal venous phase CT images demonstrated low-density solid right hepatic lobe lesions with no calcifications (Fig. 1).

MRI findings show multiple hepatic nodules, with the 3 most extensive located in the VII and anterior and posterior VI hepatic segments. All nodules present with mainly intermediate signal on T2 (Fig. 2) and intratumoral fat content (Fig. 3), without diffusion restriction.

In dynamic evaluation after Gadolinium administration, the nodules demonstrated intense enhancement in the arterial phase with washout in portal and equilibrium phases, except for the lesion in the anterior segment VI, which did not show washout in portal and equilibrium phases (Fig. 4). The imaging characteristics of these adenomas are indicative of the HNF1 alpha-inactivated subtype. No lesions of the biliary tract were detected.

After the imaging findings indicated hepatic adenomas, it was decided to follow-up without biopsy, surgical or pharmacological interventions for now.

Discussion

Hepatocellular adenomas are rare benign neoplasms arising from hepatocytes, occurring at a rate of 3-4 per 100,000 [1]. Among men, the incidence is even lower. Risk factors for the development of HCAs include oral contraceptives, androgen hormone imbalance, obesity, alcohol intake, antiepileptic drugs, liver vascular disease, chronic viral hepatitis, cirrhosis, previous malignancy, and germline genetic susceptibility [1–3].

Although HCAs are considered benign, these lesions have the potential for complications, with severe bleeding, rupture, and malignant transformation [1,8].

Currently, subtypes of HCAs are Inflammatory, HNF-1α, β-catenin-mutated family (β-catenin–mutated exon 3, Mixed inflammatory and β-catenin–mutated exon 3, β-catenin–mutated exon 7/8, Mixed inflammatory and β-catenin–mutated exon 7/8), Sonic hedgehog, and Unclassified [4].

In our case, we demonstrated some small hepatocellular adenomas whose imaging characteristics indicate the HNF-1α HCA subtype, with no signs of malignant transformation.

Rasmussen's encephalitis is a progressive disease characterized by drug-resistant focal epilepsy, progressive hemiplegia, and cognitive decline, with unihemispheric brain atrophy [5]. The disorder is rare and affects mostly children or young adults [5].

Antiepileptic drugs have a limited effect on seizures and disease progression in Rasmussen's encephalitis [5]. A realistic aim of antiepileptic drug therapy in Rasmussen's encephalitis should be to protect the patient from the most severe seizures, namely bilateral convulsive seizures, rather than to achieve seizure freedom [5]. Treatment should, therefore, be adjusted to achieve optimum seizure control with the fewest side effects [5].

The association between hepatic adenomas and antiepileptic drugs is not new in laboratory mice and rats, where phenobarbital and oxcarbazepine have been used to promote hepatic tumorigenesis, including hepatic adenomas [2,7].

The hepatocarcinogenicity mechanism of phenobarbital was that the agent, through the cytochrome P450 system, induced the conversion of xenobiotics to carcinogen activated compounds [6]. Recently, many authors, however, have hypothesized that phenobarbital could have a tumor-promoting effect inhibiting the hepatocyte gap junctional intercellular communication, and this correlates with specific hepatocarcinogenicity [6].

Phenobarbital was administered to our patient for 26 years, and the long-term use of antiepileptic drugs may have persistently induced mild but significant damage as well as continuous regenerative changes of these hepatocytes, resulting in neoplastic transformation. Therefore, long-term use of phenobarbital might have contributed to the development of hepatocellular adenomas in this case.

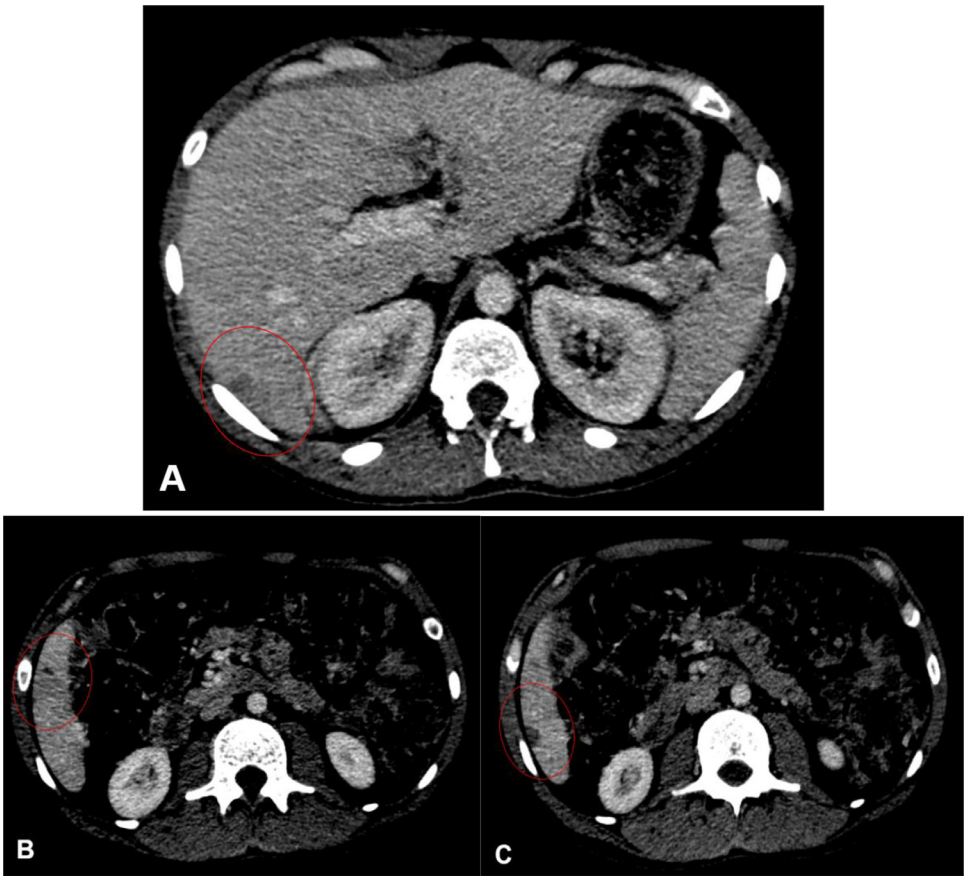

Fig. 1 – CT Portal venous phase demonstrates peripheral hypodense liver nodules (circles).

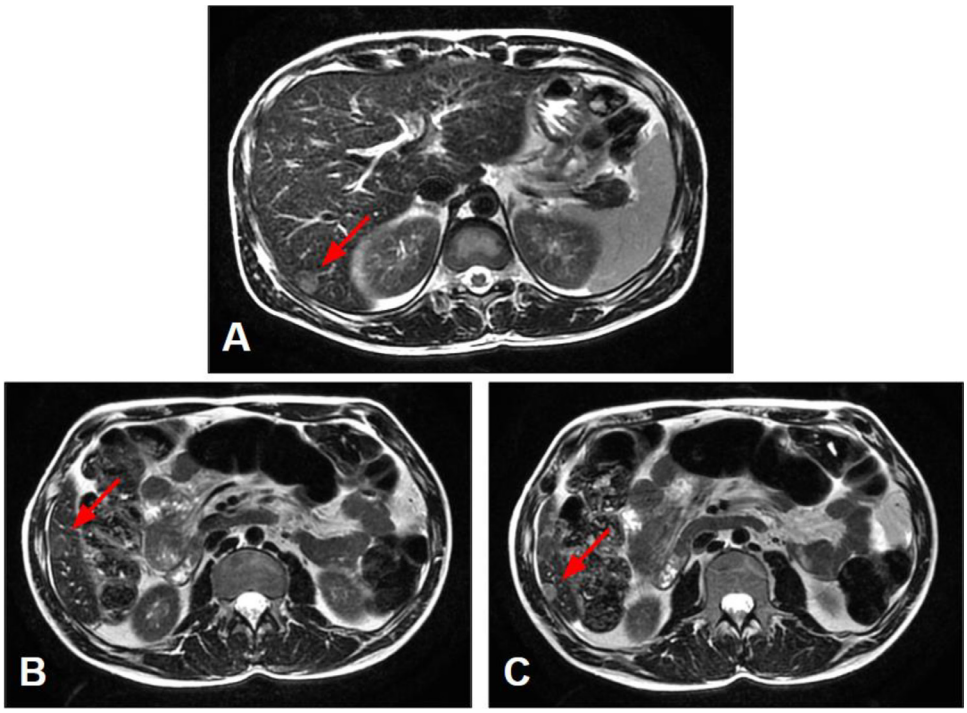

Fig. 2 – Axial FSET2 W images. There are 3 circumscribed slight hyperintense lesions (arrows).

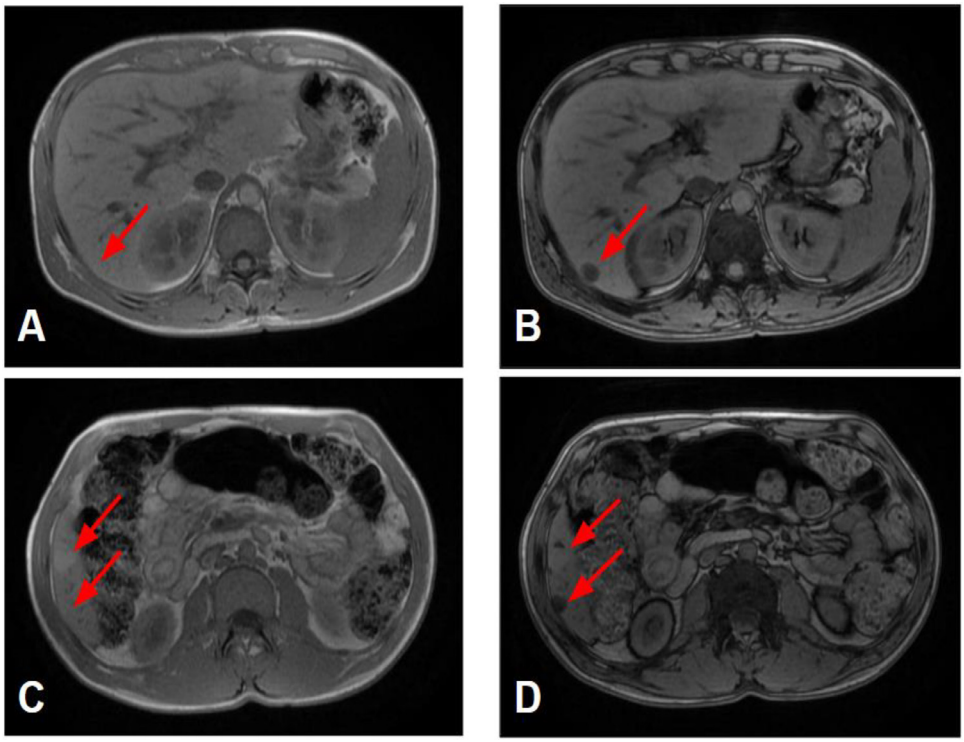

Fig. 3 – GRET1 W in- and out-phased images. The same lesions are mainly isointense in T1 W in-phase (arrows in A and C) and demonstrate marked diffuse chemical shift signal intensity loss (arrows in B and D).

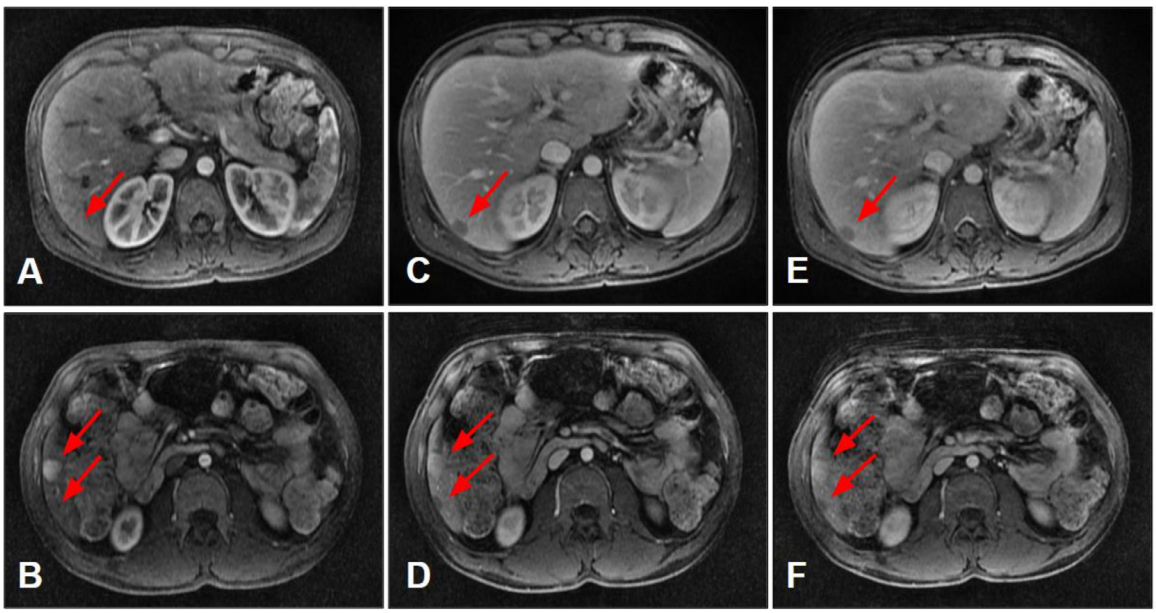

Fig. 4 – In dynamic evaluation after Gadolinium administration, the lesions of segments VII e posterior segment VI show intense enhancement in the arterial phase (A and B) with washout in the portal (C and D) and equilibrium (E and F) phases. The lesion anterior segment VI shows intense enhancement in the arterial phase (A and B) without washout in the portal (C and D) and equilibrium (E and F) phases.

We herein reported the diagnostic imaging findings of a case of hepatocellular adenoma in a 32-year-old man with Rasmussen syndrome. The patient has been using antiepileptic drugs for an extended period with no history of either anabolic or androgenic steroid use. No other predisposing risk factor for hepatocellular adenomas was found, excluding other causal possibilities besides antiepileptic drugs.

Although this association is well known, interpretation can be challenging due to the rarity of the case. Until then, it is not known which subtype of hepatic adenoma is most commonly associated with the chronic administration of antiepileptic drugs, nor the rate of related complications and, mainly, malignancy. Never forget that hepatic adenomas are uncommon in men, mainly if they have not used androgenic steroids. Therefore, always remember to verify antiepileptic drug use, as these may be a risk factor, mainly if used for long periods.

Declaration of AI and AI-assisted technologies in the writing process

Generative AI was used to improve the manuscript.

Patient consent

Verbal and written informed consent were obtained from the patient's guardian to use the images for publication.

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