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Spontaneous hepatic hemorrhage associated with multiple hepatocellular adenomas: Case report

Hemorragia hepática espontánea asociada a múltiples adenomas hepatocelulares: reporte de caso

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Abstract

Hepatocellular adenoma is a rare benign neoplasm that predominantly affects females, with an increased incidence linked to oral contraceptive use. These tumors are associated with a risk of malignancy and can result in rupture, leading to spontaneous hepatic hemorrhage. This report presents a 28-year-old female on oral contraceptives with an acute abdomen. Multiple hepatocellular adenomas were identified, the largest measuring 8 cm and showing signs of previous rupture. Given this situation, the patient successfully underwent partial hepatectomy and cholecystectomy to resolve the condition. This case highlights the importance of evaluating the acute abdomen to identify hemorrhagic causes and manage complications effectively.

Keywords: acute abdomen; general surgery; hepatectomy; liver neoplasms; liver cell adenoma.

Resumen

El adenoma hepatocelular es una neoplasia benigna poco frecuente que afecta predominantemente al sexo femenino y cuya incidencia aumenta con el uso de anticonceptivos orales. Estos tumores se asocian con riesgo de malignidad y pueden llegar a romperse, lo que lleva a una hemorragia hepática espontánea. En este informe se presenta el caso de una mujer de 28 años que tomaba anticonceptivos orales y presentaba abdomen agudo. Se identificaron múltiples adenomas hepatocelulares, el mayor de los cuales medía 8 cm y mostraba signos de rotura previa. Ante esta situación, la paciente fue sometida con éxito a una hepatectomía parcial y colecistectomía para resolver la afección. Este caso resalta la importancia de evaluar el abdomen agudo para identificar causas hemorrágicas y manejar las complicaciones de manera efectiva.

Palabras clave: abdomen agudo; cirugía general; hepatectomía; neoplasias hepáticas; adenoma de células hepáticas.

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Introduction

Hepatocellular adenoma, also called hepatic adenoma (HA), is a rare benign epithelial neoplasm that predominantly affects females during their reproductive years (Wang & Zhang, 2022; Cacciatori et al., 2023). This tumor is strongly associated with oral contraceptives (OC) use due to the risk posed by exogenous estrogen exposure (Wang & Zhang, 2022). In addition to estrogen, other risk factors include obesity, fatty liver disease, hepatic vascular disorders, and the use of anabolic-androgenic steroids (Hui & Lee, 2019; Tomihara et al., 2021; Wang & Zhang, 2022). Although they are considered benign, HAs are associated with risks of complications, such as malignant transformation into hepatocellular carcinoma, rupture, and spontaneous hepatic hemorrhage, a rare complication highlighted in this study (Srinivasa et al., 2015; Mathew et al., 2019; Renzulli et al., 2019; Mouhoub et al., 2020; Shreenath et al., 2024).

Case Report

A 28-year-old female patient, with no comorbidities, no history of previous surgeries or pregnancies, and using OC, presented to the hospital with abdominal pain that had started 5 days earlier,

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accompanied by a reported sensation of weakness. On physical examination, she was pale (+/5), afebrile, and hemodynamically stable, with a capillary refill time of less than three seconds and a heart rate of 110 bpm. There was pain in the left hypochondrium on abdominal palpation without signs of peritoneal irritation. The initial management included analgesia, intravenous hydration, and laboratory and imaging assessments. Upon admission, laboratory tests revealed anemia, thrombocytosis, and elevated C-reactive protein (CRP) levels, as detailed in Table 1. A computed tomography scan of the whole abdomen performed on the first day demonstrated heterogeneous nodular lesions along the lateral border of the left hepatic lobe, measuring 101 × 74 mm, and the inferior border of the right hepatic lobe, measuring 62 × 52 mm, suggestive of hepatocellular-origin liver damage. Additionally, a small amount of free fluid was detected in the pelvis, supporting the initial diagnostic hypothesis of acute hemorrhagic abdomen due to HA rupture. On the second day of hospitalization, the patient experienced relief from abdominal pain and remained hemodynamically stable. Laboratory tests showed an increase in hemoglobin levels following the transfusion of one unit of red blood cells, accompanied by a rise in indirect and total bilirubin levels. At the same time, the international normalized ratio (INR) remained within the normal range, as shown in Table 1.

Table 1: Admission laboratory tests and laboratory tests during hospital stay

Tests	Day of admission	Day 2	Second postoperative day	Hospital discharge	Reference
Hemoglobin (g/dL)	8.9	10.3	11.2	11.8	12.0 to 16.0
Leukocytes (µL)	9,300	9,600	17,100	14,000	3,500 to 10,000
Platelets (µL)	596,000	603,000	574,000	613,000	150,000 to 450,000
INR	0.81	0.87	0.85	0.9	0.8 to 1.2
Indirect Bilirubin (mg/dL)	0.64	1.03	-	0.33	0.2 to 0.8
Total Bilirubin (mg/dL)	0.88	1.95	-	0.49	< 1.00
Creatinine (mg/dL)	0.7	0.55	0.56	0.47	0.50 to 1.10
CRP (mg/dL)	23.75	-	25.03	13.84	< 1.00
Beta - HCG Quantitative (mUI/mL)	< 1.2	-	-	-	Above 5.0: indicating pregnancy

Abbreviations: CRP = C-reactive Protein; INR = International Normalized Ratio.

Magnetic resonance imaging (MRI) of the upper abdomen, performed on the fourth day of hospitalization with paramagnetic gadolinium contrast, revealed a heterogeneous liver due to hypervascular liver lesions suggestive of HA, as shown in Figure 1. The identified lesions were as follows: 1. Located in segment II/III, with signs of intralesional bleeding, measuring 8.2 cm; 2 and located in segment IVb, measuring 5.0 cm; 3. Located in segment VI, measuring 6.0 cm; 4 and located in the VIII/V segment, measuring 4.1 cm; 5. Located in segment VI/VII, measuring 2.8 cm; 6. Located in segment VI, measuring 1.7 cm; 7 and located in segment VII, measuring 1.6 cm.

After the tests, a second unit of packed red blood cells was transfused, and the surgical planning was maintained.

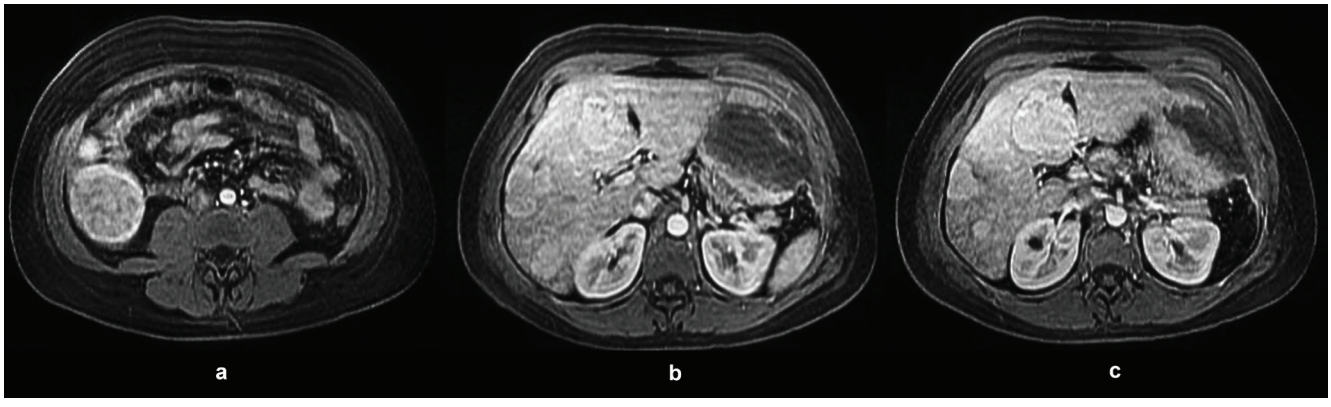

Figure 1: MRI of the upper abdomen (T1-weighted fat-suppressed sequence with gadolinium contrast in the arterial phase), showing multiple hypervascular hepatic lesions consistent with hepatocellular adenomas (HA). (a) The early arterial phase, with heterogeneous enhancement and hyperintensity and hypointensity areas, indicates active hemorrhage and thrombus formation. (b) Intermediate arterial phase, with progressive contrast uptake and improved delineation of intralesional hemorrhage. (c) Late arterial phase, characterized by more homogeneous contrast distribution and better differentiation between the lesions and surrounding liver tissue.

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On the seventh day of hospitalization, the patient underwent conventional surgery. During the inspection of the abdominal cavity, multiple hepatic nodules were identified, the largest of which measured approximately 8 cm in the left hepatic lobe, with signs of previous rupture; another pedunculated nodule was found in the right lobe, measuring approximately 6 cm; and there were no other changes in the abdominal cavity (Figure 2). A partial hepatectomy involving segments II, III, and VI was performed, along with a cholecystectomy to enhance visualization of the liver surface and the nodules located inferior to the gallbladder. The specimens were sent to the pathology department (Figure 2).

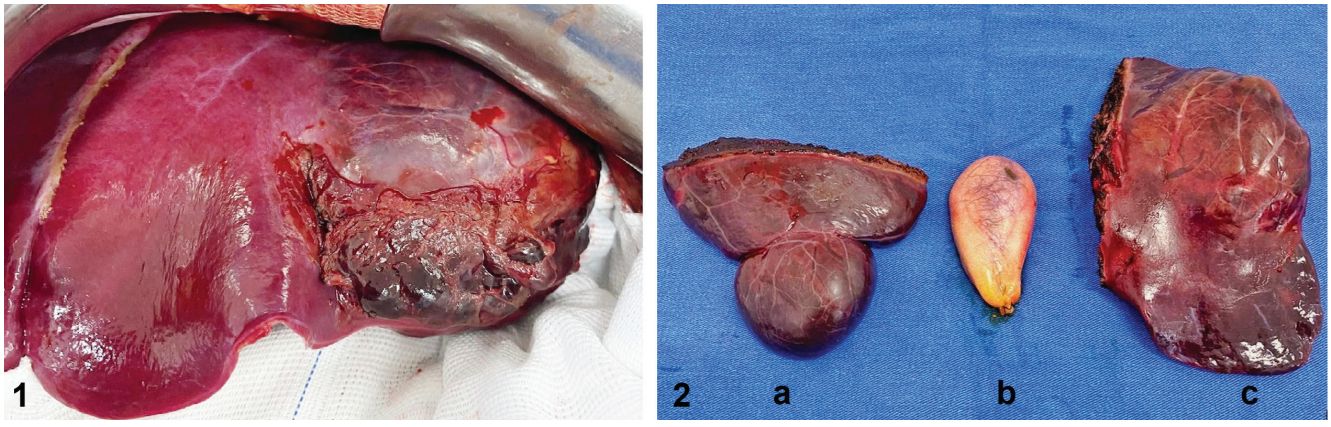

Figure 2: 1: Image of the abdominal cavity, showing the hepatic nodule in segments II and III with signs of previous bleeding. 2: Specimens sent for histopathological analysis. (a) Product of partial hepatectomy of segment VI. (b) Product of cholecystectomy. (c) Product of partial hepatectomy of segments II and III, with a hemorrhagic and friable appearance.

On the first postoperative day, the patient showed favorable progress in the intensive care unit (ICU), being painless at rest and with well-tolerated oral intake. She reported pain upon palpation in the left hypochondrium, but there were no signs of peritoneal irritation. The surgical wound from laparotomy performed using a Makuuchi incision appeared well, with coapted edges and small amounts of serosanguineous secretion in the cavity drain. On the second postoperative day, she was discharged from the ICU with no alarming signs. As shown in Table 1, laboratory tests revealed an improvement in hemoglobin levels, along with an increase in leukocytosis and CRP.

On the fifth postoperative day, the patient was discharged from the hospital. Laboratory tests showed a reduction in leukocytosis and CRP (Table 1). A follow-up appointment was scheduled for seven days later. She was advised to stop using OC, and after six months, a new MRI revealed a reduction in the size of HAs, the largest of which was in segment IVb, measuring 4.3 cm. The histopathological examination revealed no signs of malignancy in the analyzed sections but showed evidence of prior hemorrhage, organized hematoma, sinusoidal congestion, and subcapsular hemorrhage, as depicted in the histological image in Figure 3.

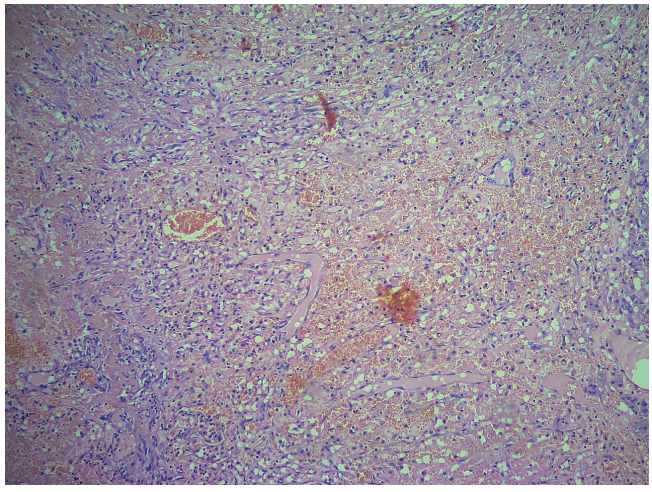

Figure 3: Histological image showing organized hematoma, sinusoidal congestion, and subcapsular hemorrhage in the resected liver parenchyma.

Discussion

HAs are benign and rare hepatic epithelial tumors, representing approximately 2% of all liver tumors. An HA is solitary in 80% of cases and is most frequently located in the right hepatic lobe (Dokmak et al., 2009; Mathew et al., 2019; Shreenath et al., 2024). HAs are more prevalent among women of reproductive age, particularly among those using OC for more than 5 years, with an estimated rate of three to four

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women affected per one hundred thousand inhabitants, compared to the incidence in the general population, which affects one person per 1 million inhabitants (Shreenath et al., 2024; Taj et al., 2020).

Furthermore, it has been observed that stopping the use of OC results in a reduction of approximately 30% in the size of tumors in many patients (Shah et al., 2023). This is similar to the findings reported by Moors et al. (2021), as multiple HAs showed a decrease in number and size after discontinuing OC use.

In addition to the well-established risk associated with the use of exogenous estrogen, several other factors contribute to the development of these tumors. These include the use of anabolic-androgenic steroids, recombinant human growth hormone, obesity, fatty liver disease, glycogen storage disorders, hepatic vascular abnormalities, and genetic predispositions (Hui & Lee, 2019; Tomihara et al., 2021; Wang & Zhang, 2022; Shreenath et al., 2024).

Hepatocellular adenomas can be classified into four main subtypes based on their genetic and histological characteristics: Inflammatory Hepatocellular Adenomas (IHCA, 40-50% of cases), Hepatocyte Nuclear Factor-1-alpha (HNF1-alpha, 35-40% of cases), Beta-catenin-Activated Mutations (15-20% of cases), and the Unclassified Type (10% of cases) (Shreenath et al., 2024). Beta-catenin, a crucial component of the Wnt signaling pathway that regulates cell proliferation and differentiation, contributes to developing more aggressive adenomas when mutated, particularly in exon 3 of its gene (Gao et al., 2017). These mutations are associated with larger tumor size, a higher risk of malignant transformation into hepatocellular carcinoma, and a greater likelihood of hemorrhagic complications (Shreenath et al., 2024). Although molecular confirmation was not obtained in the present case, the tumor's considerable size and associated hemorrhage strongly suggest a beta-catenin-mutated subtype.

Regarding the macroscopic appearance of HA, the specimens obtained from the patient in this study (Figure 2) align with the characteristics described in the literature by Shreenath, et al. (2024). These features include color variation, ranging from light brown to yellow, a soft texture, and well-defined borders without a true capsule. Additionally, HAs consist of hepatocytes with significant vascularization and the absence of bile ducts, which distinguishes them from the surrounding normal liver tissue (Shreenath et al., 2024).

Approximately half of the patients with HA are asymptomatic, and the condition is often discovered incidentally during imaging studies. However, some patients may report mild, poorly defined abdominal pain and abdominal distension (Shreenath et al., 2024). The sudden rupture of these tumors can lead to spontaneous hepatic hemorrhage, resulting in sharp, intense abdominal pain due to bleeding. This complication may cause serious consequences, including hypotension, hypovolemic shock, and even death (Srinivasa et al., 2015; Mathew et al., 2019; Tomihara et al., 2021; Shreenath et al., 2024;). Another potential outcome of HA is malignant transformation into hepatocellular carcinoma, which occurs in 4.2% of patients (Mathew et al., 2019).

According to Cacciatori et al., (2023), lesions located in hepatic segments II and III exhibit a greater propensity for bleeding. This observation aligns with the findings in the present study, where segments II and III showed evidence of bleeding, including at the site of the largest HA. This complication is associated with a high mortality rate, occurring in up to 27% of cases, typically in tumors larger than 5 cm (Cacciatori et al, 2023; Shreenath et al., 2024).

From this perspective, given the severity of HA rupture, initial management in emergency situations is recommended, including hemodynamic resuscitation and correction of potential coagulation disorders (Cacciatori et al, 2023). In hemodynamically stable patients, selective hepatic arterial embolization may be performed, along with further investigation of the lesion, for which MRI is preferred (Cacciatori et al, 2023). MRI assists in diagnosis, planning, and evaluating the need for surgery (Tomihara et al., 2021; Cacciatori et al, 2023). In cases of hepatocellular adenomas with beta-catenin mutations, which carry a higher risk of complications, strategies such as selective hepatic arterial embolization, radiofrequency ablation, and transcatheter arterial embolization can be effective in controlling hemorrhage and avoiding more invasive interventions (Ponnatapura et al., 2019). These endovascular approaches, combined with rigorous follow-up imaging, enable safer management, particularly for lesions that are difficult to resect or in patients with clinical and genetic characteristics that increase the risk of complications (Moors et al., 2021; Shreenath et al., 2024).

Strategies for managing HA vary according to each patient's risk factors and include cessation of the use of estrogen and exogenous androgens, as well as weight loss in obese patients (Haring et al., 2019; Mathew et al., 2019). In general, as Mathew et al. (2019) described, hepatocellular adenomas smaller than 5 cm, which do not present symptoms, are initially approached conservatively, as they generally follow a benign course and have a low risk of complications. In this scenario, regular follow-up every 6 months through imaging exams is recommended (Mathew et al., 2019; Taj et al., 2020).

In the case presented, surgical intervention was the procedure of choice due to adenomas in the patient, which exceeded 5 cm in diameter, were associated with bleeding, and posed a risk of adverse events. Accordingly, surgical resection is recommended

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for female patients with tumors larger than 5 cm, while for male patients, it is recommended regardless of tumor size (Dokmak et al., 2009; Mathew et al., 2019; Taj et al., 2020; Shreenath et al., 2024). The procedure does not require wide safety margins and elective surgery is associated with a mortality rate of less than 1% (Shreenath et al., 2024). However, in cases that require an emergency surgical approach due to hemodynamic instability resulting from adenoma rupture, the mortality rate may increase up to 10 times (Cacciatori et al, 2023; Shreenath et al., 2024).

Conclusions

Hepatocellular adenomas are rare and benign liver tumors that have the potential to become malignant or rupture. Due to these possible complications, it is essential to carry out periodic monitoring of these neoplasms, and, in case of acute events, it is necessary to plan the most appropriate approach for the patient. This report demonstrates a case of a spontaneous hepatic hemorrhage caused by an adenoma with previous signs of rupture associated with multiple adenomas. This reinforces the need for surgical intervention, which includes ceasing the use of oral contraceptives.

Recognitions

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Authors Contributions:

Conception: Leandro Billó, Nicoly Camila Spack, Bruno Landal Cavassin. **Research:** Bruno Landal Cavassin, Alan dos Santos Camargo, Odair de Sousa Neto. **Supervision:** Leandro Billó, Francisco Emanuel de Almeida. **Redaction (original version):** Nicoly Camila Spack, Bruno Landal Cavassin. **Redaction (revision and editing):** Leandro Billó, Nicoly Camila Spack, Bruno Landal Cavassin, Alan dos Santos Camargo, Odair de Sousa Neto, Francisco Emanuel de Almeida.

References

Cacciatori FA, Rodrigues PD & Fontes PRO. (2023). Bleeding hepatocellular adenoma: historical series and outcomes. *Revista do Colégio Brasileiro de Cirurgiões* **50**, e20233549. https://doi.org/10.1590/0100-6991e-20233549-en

Dokmak S, Paradis V, Vilgrain V, Sauvanet A, Farges O, Valla D, *et al*. (2009). A single-center surgical experience of 122 patients with single and multiple hepatocellular adenomas. *Gastroenterology* **137**(5), 1698-1705. https://doi.org/10.1053/j.gastro.2009.07.061

Gao C, Wang Y, Broaddus R, Sun L, Xue F, Zhang W. (2017). Exon 3 mutations of CTNNB1 drive tumorigenesis: a review. *Oncotarget* **9**(4), 5492-5508. https://doi.org/10.18632/oncotarget.23695

Haring MPD, Gouw ASH, de Haas RJ, Cuperus FJC, de Jong KP & de Meijer VE. (2019). The effect of oral contraceptive pill cessation on hepatocellular adenoma diameter: A retrospective cohort study. *Liver international: official journal of the International Association for the Study of the Liver* **39**(5), 905–913. https://doi.org/10.1111/liv.14074.

Hui CL & Lee ZJ. (2019). Hepatic disorders associated with exogenous sex steroids: MR imaging findings. *Abdominal Radiology (New York)* **44**(7), 2436–2447. https://doi.org/10.1007/s00261-019-01941-4

Mathew RP, Manolea F, Girgis S, Patel V & Low G. (2019). Malignant transformation of hepatic adenoma complicated by rupture and hemorrhage: An extremely rare clinical entity. *Intractable Rare Diseases Research* **8**(4), 266-270. https://doi.org/10.5582/irdr.2019.01089

Moors G, Poels H, Vandecaveye V, Roskams T & Verslype C. (2021). Regression of multiple hepatocellular adenomas after cessation of oral contraceptive pills: a case report and review of the current literature. *Acta Gastroenterologica Belgica* **84**, 505-508. https://doi.org/10.51821/84.3.017

Mouhoub M, Miry A, Haloui A, Karich N, Kamaoui I, Soufi M, *et al.* (2020). Malignant transformation of hepatocellular adenoma: report of a case. *Pan African Medical Journal* **26**, 35-92. https://doi.org/10.11604/pamj.2020.35.92.17416

Ponnatapura J, Kielar A, Burke LMB, Lockhart ME, Abualruz AR, Tappouni R & Lalwani N. (2019). Hepatic complications of oral contraceptive pills and estrogen on MRI: Controversies and update - Adenoma and beyond. *Magnetic Resonance Imaging* **60**, 110-121. https://doi.org/10.1016/j.mri.2019.04.010

Renzulli M, Clemente A, Tovoli F, Cappabianca S, Bolondi L & Golfieri R. (2019). Hepatocellular adenoma: An unsolved diagnostic enigma. *World Journal of Gastroenterology* **25**(20), 2442-2449. https://doi.org/10.3748/wjg.v25.i20.2442

Shah S, Meka O, Reddy A, Neelam S & Wilcox C. (2023). A Rare Presentation of Multiple Hepatic Masses Due to Hepatic Adenoma: A Case Report. *Journal of Investigative Medicine High Impact Case Reports* **11**, 23247096231166676.

Shreenath AP, Grant LM & Kahloon A. (2024). *Hepatocellular Adenoma*. StatPearls Publishing, Treasure Island (FL).

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Srinivasa S, Lee WG, Aldameh A & Koea JB. (2015). Spontaneous hepatic haemorrhage: A review of pathogenesis, aetiology and treatment. *HPB : the official journal of the International Hepato Pancreato Biliary Association* **17**(10), 872–880. https://doi.org/10.1111/hpb.12474

Taj H, Comba I, Kumar S & Lakhinder B. (2020). Extracapsular Hepatocellular Adenoma: A Diagnostic Dilemma. *Cureus* **12**(6), e8928. https://doi.org/10.7759/cureus.8928

Tomihara H, Hashimoto K, Ishikawa H, Terashita D, Gakuhara A, Fukuda S, *et al*. (2021). Successful resection of a huge hepatocellular adenoma. *Clinical Journal of Gastroenterology* **14**, 1544-1549. https://doi.org/10.1007/s12328-021-01486-4

Wang X & Zhang X. (2022). Hepatocellular adenoma: Where are we now? *World Journal of Gastroenterology* **28**(14), 1384-1393. https://doi.org/10.3748/wjg.v28.i14.1384

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