

LARGE HEPATOCELLULAR ADENOMA OF THE LIVER IN A WOMAN OF REPRODUCTIVE AGE

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Hepatocellular adenoma is a rare benign liver tumor with the potentially unfavorable course due to the risk of hemorrhage and malignant transformation. Treatment depends on the mass subtype and size. Here we present a clinical case of hepatocellular adenoma in a woman of reproductive age developed against the background of the long-term use of oral contraceptives. The tumor sized 8 cm was detected accidentally during instrumental examination; morphological and immunohistochemistry assessment confirmed that it was a benign one without β -catenin mutation. Liver resection was performed. The case highlights the importance of careful monitoring of the patients during the long-term use of oral contraceptives, as well as of the timely surgical interventions in individuals with large hepatocellular adenomas to prevent hemorrhage and malignization.

Keywords: hepatocellular adenoma, liver tumors, estrogen-containing drugs, liver resection

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Compliance with ethical standards: the patient submitted the informed consent for publication of anonymized personal medical information.

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КРУПНАЯ ГЕПАТОЦЕЛЛЮЛЯРНАЯ АДЕНОМА ПЕЧЕНИ У ЖЕНЩИНЫ РЕПРОДУКТИВНОГО ВОЗРАСТА

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Гепатоцеллюлярная аденома является редкой доброкачественной опухолью печени с потенциально неблагоприятным течением, обусловленным риском кровоизлияния и злокачественной трансформации. Лечение зависит от подтипа и размеров образования. Представлено клиническое наблюдение гепатоцеллюлярной аденомы у женщины репродуктивного возраста на фоне длительного применения оральных контрацептивов. Опухоль размером 8 см была случайно выявлена при инструментальном обследовании; морфологическое и иммуногистохимическое исследование подтвердили доброкачественный характер без мутации β -катенина. Выполнена резекция печени. Случай подчеркивает важность внимательного наблюдения за пациентками на фоне длительного приема гормональных контрацептивов и своевременного хирургического вмешательства при крупных гепатоцеллюлярных аденомах с целью профилактики риска кровоизлияний и малигнизации.

Ключевые слова: гепатоцеллюлярная аденома, опухоли печени, эстрогенсодержащие препараты, резекция печени

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Соблюдение этических стандартов: пациент подписал добровольное информированное согласие на публикацию персональной медицинской информации в обезличенной форме.

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Hepatocellular adenoma (HCA) is a rare benign liver tumor diagnosed mainly in women of reproductive age [1, 2]. The long-term use of oral contraceptives (for more than 5 years) is the leading risk factor of HCA. The incidence of HCA in the general population is uncertain, there are reports of 0.001–0.004%. According to the literature data [3], adenomas are considerably more often diagnosed in women using oral contraceptives for the long term (3.4 cases per 100,000 population), while the rate among women not using such drugs varies between

1–1.3 per 100,000 population. There is a direct relationship between the duration of using contraceptives and the increase in the rate of developing HCA and severity of HCA clinical manifestations (patients' complaints) [3]. In recent decades, the female-to-male ratio has decreased from 11 : 1 to 4 : 1, which is associated with the increasing use of anabolic steroids [4]. Additional risk factors include glycogenosis, obesity, metabolic syndrome, alcohol abuse, and endocrine disorders, including Klinefelter syndrome, type 3 diabetes (MODY), and polycystic

ovary syndrome [5, 6]. In recent years, the HCA association with the use of clomiphene and barbiturates has been shown [4, 7].

The main HCA complications include spontaneous hemorrhage reported in 27% of cases of detecting masses sized over 5 cm [4] and malignant transformation. Hemorrhage can be intratumoral, intrahepatic or intraperitoneal; intraperitoneal hemorrhage is associated with the development of acute hemorrhagic syndrome fraught with high risk of hemorrhagic shock and fatality [5].

Male sex, β -catenin mutations (exon 3), and the tumor size over 5 cm are associated with the increased risk of HCA malignization [8, 9].

In terms of morphology, HCAs consisting of hepatocytes without portal tracts and bile ducts are supplied by arteries only [2]. Due to the limited diagnostic information content of standard histological examination, especially when used for differential diagnosis of subtypes of HCA and hepatocellular carcinoma, immunohistochemistry and molecular genetic methods become increasingly important [10–12]. In 2007, the key immunohistochemistry markers for HCA classification were proposed, including L-FABP, β -catenin, glutamine synthetase, and serum amyloid A [13]. However, these proteins can be expressed in other benign and malignant liver lesions. Therefore, it is necessary to assess the nature of their distribution in the context of the background liver tissue [2]. Thus, the HCA diagnosis requires consistent, comprehensive assessment of clinical data, instrumental testing results, as well as morphological and immunohistochemical verification of the mass.

In 2017, the analysis of more than 500 HCA cases showed the correlation of molecular and immunohistochemical subtypes with the risk of hemorrhage, tumor growth, and malignant transformation [4]. The authors expanded classification to eight subtypes, including different variants of β -catenin-activated adenomas, mixed forms, sonic Hedgehog signaling adenoma (sh-HCA), associated with intratumoral hemorrhage [4, 14]. In total, novel and unclassified subtypes constitute about one third of all HCAs.

Thus, the current data emphasize the importance of comprehensive approach to the HCA diagnosis and risk stratification including clinical assessment, instrumental tests (MRI, CT, ultrasonography), and immunohistochemistry, which directly reflects the patient management strategy presented in this case study.

Clinical case

Patient M. aged 28 presented with the right hypochondrial pain, pressure in her epigastric region, and cough with a small amount of sputum that emerged after acute respiratory viral infection. She had a history of gastro-esophageal reflux disease and the long-term (more than 10-year) use of combined oral contraceptives. She had no family history of cancer of liver disease. The patient denied occupational hazards and the exposure to adverse production factors.

Assessment performed in a medical institution in Donetsk occasionally revealed a liver mass. The patient contacted the oncologic dispensary in Rostov-on-Don on her own for further diagnosis and comprehensive assessment.

Assessment data

According to the abdominal magnetic resonance imaging (03.10.2025, revision 05.10.2025), the liver is enlarged, with

an uneven outline; bilobar dimensions 208 × 186 mm. A solid mass sized at least 65 × 76 × 80 mm in the S5–S6 segments is visible, which is comparable with the intact liver parenchyma based on signal intensity, with contrast uptake. When performing differential diagnosis, we considered focal nodular hyperplasia, hepatocellular adenoma, and hepatocellular carcinoma. The diagnostic interpretation was difficult due to technical limitations of the study (low signal-to-noise ratio, no full-fledged arterial phase and wash-in/wash-out phases). No ascites detected, bone structures without signs of abnormality.

The clinical and laboratory tests conducted revealed no abnormality. The alpha-fetoprotein (AFP) level of 2.36 ng/mL was within the reference range.

Due to the patient's young age, no liver cirrhosis, AFP within the reference range, the presence of the large solid mass, and inability to reliably rule out both benign and malignant nature of the tumor based on radiological data, it was decided to perform trephine biopsy in order to morphologically verify the diagnosis, which was of fundamental importance for determination of further treatment tactics.

The biopsy specimen histological examination (19.10.2025) revealed hepatocytes showing signs of focal protein (granular) dystrophy; some cells were deformed and atrophic. There were no portal tracts. Morphological features corresponded to hepatocellular adenoma (ICD-10: D13.4). Considering the need for malignization risk stratification, immunohistochemistry (IHC) assessment aimed at estimating proliferation activity and detecting β -catenin mutation was recommended.

According to IHC data (19.10.2025), the Ki-67 index was 2%, which suggests low proliferation activity of tumor cells. There was no nuclear β -catenin expression, which allowed us to rule out the β -catenin-activated adenoma subtype associated with high risk of malignization. Thus, IHC assessment confirmed that the mass was benign and belonged to the group of low cancer risk.

The morphological and immunophenotyping data obtained (no signs of β -catenin activation and low Ki-67 index) allowed us to consider the tumor as benign. At the same time, considerable tumor size (over 5 cm), risk of spontaneous bleeding, and the long-term use of oral contraceptives as a potential etiological factor made surgical treatment feasible.

On 07.11.2025 the patient underwent elective surgery with endotracheal anesthesia and intraoperative monitoring of vital functions. Midline laparotomy with layer-by-layer dissection of the anterior abdominal wall tissues was performed. After dissection the abdominal cavity was thoroughly revised: no free fluid was detected, no signs of tumor dissemination or peritoneal lesion were found. The liver was enlarged, in the projection of segments VI–VII there was a soft elastic mass with a diameter up to 8–9 cm (Fig.). Considering the tumor localization and size, anatomic resection of the liver segments VI–VII was performed using an ultrasonic scalpel and waterjet dissector, within the limits of visually intact tissues. The liver wound was treated using an argon plasma coagulator and hemostatic sponge (Tachocomb, Austria). A drainage tube made of polyvinyl chloride was installed in the subhepatic space. The abdominal cavity was sutured layer by layer. The radical surgery was performed without any technical complications.

The resected material morphological examination has shown that the mass is partially encapsulated and has uneven outline. It is represented by beams formed by two cell layers surrounded by the well-developed reticulin framework; there are no portal tracts. Morphological features correspond to hepatocellular adenoma.

The data obtained has confirmed that the resected liver mass was the HCA showing no signs of nuclear β -catenin activity.

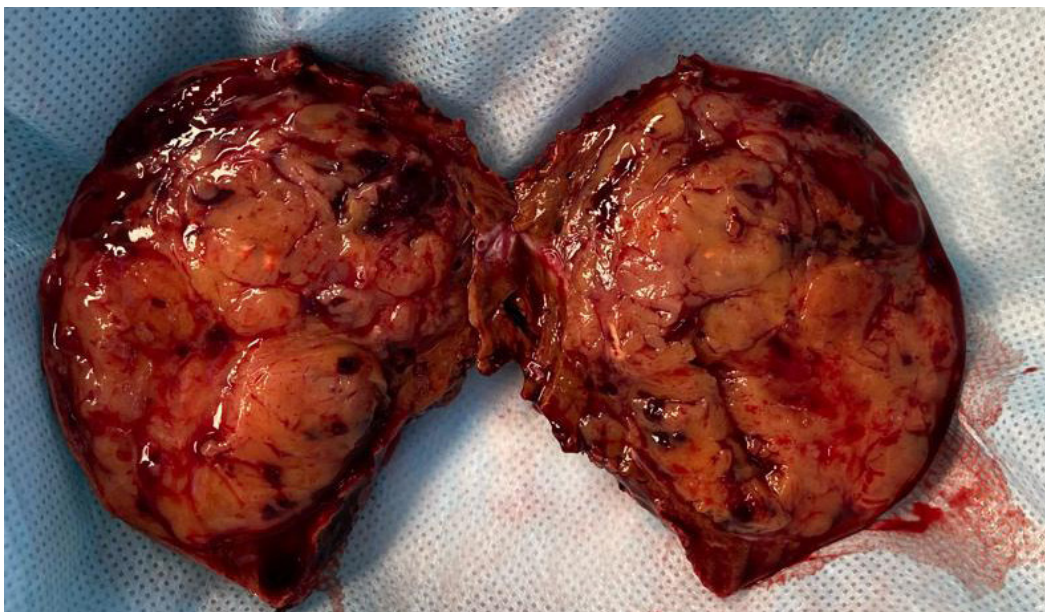


Fig. Gross specimen. Liver tissue fragment sized 8 × 8 × 7 cm, at a distance of 1 cm from the nearest resection margin

Morphological verification of biopsy and resected materials revealed typical HCA architecture with the beams of two cell layers, well-developed reticulin framework, and the lack of portal tracts. According to the immunophenotyping results, the Ki-67 index is 2%, there is no nuclear β -catenin activity, which corresponds to the group at low risk of malignization. These signs that are prognostically favorable confirm the tumor benign nature.

The postoperative period was uneventful, the patient was discharged on day 7 after surgery in satisfactory condition.

Clinical case discussion

Modern concepts emphasize heterogeneity of this group of neoplasms, differences between their molecular subtypes, and variability of prognostic characteristics. In the literature, the long-term use of oral contraceptives is considered as one of the factors associated with HCA in women of child-bearing age. In the case reported, the patient received hormonal contraceptives throughout 10 years, which can be considered a significant predisposing factor. However, the case report descriptive nature does not allow us to draw causal conclusions. The long-term hormonal exposure is associated with the increased expression of proliferative and metabolic pathways in hepatocytes, contributing to the development of adenomatous nodules. The tumor size over 5 cm remains the key prognostic criterion associated with the increased likelihood of hemorrhagic complications, regardless of the molecular subtype. It is also characterized by high risk of rupture, especially in pregnancy and during menstruation, which results in life-threatening complications [4, 9]. In large-scale clinical trials, the rate of rupture with intraperitoneal hemorrhage reached 17.5% [11].

In the clinical case reported, the patient's tumor size reached 8 cm, which corresponded to the critical size associated with the

increased risk of intrahepatic and intraperitoneal hemorrhage, especially during hormonal stimulation. Immunohistochemistry assessment revealed the lack of the β -catenin, reducing the risk of malignant transformation, but the large tumor size itself represents an indication for surgical intervention.

Establishing the final diagnosis became possible due to coherent and comprehensive assessment of clinical data, radiological test results, and morphological and immunohistochemistry verification of the mass. Integration of clinical/instrumental and pathomorphological data enabled substantiated differential diagnosis of a focal liver lesion and determination of rational treatment tactics.

CONCLUSION

HCA is a rare benign liver tumor characterized by the risk of hemorrhagic complications and malignization. The long-term use of oral contraceptives by women of child-bearing age is considered as a significant etio-pathogenetic factor, which results in the need for personalized approach to management of patients and regular monitoring of benign focal liver masses. The tumor size ≥ 5 cm is an independent predictor of unfavorable course and indication for surgery, regardless of the β -catenin mutation status. Anatomic resection of the liver in individuals with large HCAs represents a rational treatment strategy aimed at reducing the risk of life-threatening conditions and achieving favorable treatment outcomes.

The case focuses on the need for increased clinical suspicion of liver tumors in women of reproductive age, especially in cases of the long-term use of hormonal contraceptives. The lack of specific clinical and laboratory manifestations does not preclude the existence of the tumor and requires in-depth assessment with morphological verification in cases of diagnostic uncertainty.

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