Rare subtype of hepatoblastoma in a young adult: difficulties in the histopathological differentiation from hepatocellular carcinoma

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ABSTRACT

Background: Hepatoblastoma is a primary malignant tumor of the liver usually occurring in children, whereas it is very rare in adults, affecting males slightly more.

Case Presentation: We report a case of a 20-year old female patient with a palpable liver mass and significantly elevated alpha-fetoprotein (AFP), Serum Glutamic Oxaloacetic Transaminase, and Serum Glutamic-Pyruvic Transaminase values. The microscopic examination revealed a mixed cell population of small cells with an oval-shaped nucleus and scant relatively basophilic cytoplasm co-existing with larger cells with eosinophilic or clear cytoplasm, round nuclei, arranged in trabeculae of six or more cells separated by thin fibrous septa. The immunohistochemical assessment of the tumor cells revealed positivity for AFP, Glypican-3, Glutamate Synthetase, polyclonal Carcinoembryonic antigen, Cytokeratin (CK8/18), and Epithelial Specific Antigen/Ep-CAM, membranous and focally nuclear positivity for b-catenin, focal positivity for CK19 and vimentin and faintly focal positivity for Sal-like protein-4 and Cluster Differentiation 99. The cell proliferation rate Ki-67 was high, at about 85% and concerning the prognostic markers, there was a positive expression of Cyclin D1 at approximately 80% of the tumor cells, whereas c-myc was negative. These findings drove us to the diagnosis of hepatoblastoma, macrotrabecular subtype.

Conclusion: Although the age, medical history, clinical findings, and the laboratory investigations of the patient suggested hepatocellular carcinoma, on the histological examination the mixed blastematous morphology of the tumor combined with the results of the immunohistochemical assay, lead to the diagnosis of hepatoblastoma.

Keywords: Age, liver, hepatoblastoma, hepatocellular.

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Background

Hepatoblastoma is a malignant liver tumor most commonly occurring in children, whereas it is extremely rare in adults. In the literature, there are only 72 reported cases of adult hepatoblastomas till 2019, including our case [1]. The age distinction between hepatoblastoma of children and adults is still controversial; as de Bree et al. [2] stated it at 15 years of age while Rougemont et al. [3] at 17 years. However, the mean age at the diagnosis of Adult Hepatoblastoma is estimated at 42 years [4]. There is an equal proportion of males and females [4]. The prognosis of adult hepatoblastoma is poor; 1-year survival rates are estimated between 24% and 40%, in contrast to the much better prognosis in children with 10-year survival rates of 87% [5].

We presented a case of a 20-year old woman with a liver mass, and we reviewed the literature concerning the diagnostic difficulties in the histopathological differentiation of adult hepatoblastoma from hepatocellular carcinoma.

Case Presentation

A 20-year-old female patient was reported with a mass approximately 10 cm in maximum diameter at the region of the hepatic hilum. It was referred that the tumor encased but not infiltrated the ureter, pushed the bile ducts, and extended to the retroperitoneal region. Laboratory investigation revealed a very elevated alpha-fetoprotein (AFP) (>4,000 ng/ml), Serum Glutamic Oxaloacetic Transaminase, and Serum Glutamic-Pyruvic Transaminase values, whereas there was no evidence of infection by hepatitis viruses.

The histological examination of the mass revealed a mixed tumor cell population consisting of two subpopulations; embryonal and predominantly of fetal tumor cells (Figure 1). The first one was about concerning immature, small cells, with oval-shaped nuclei and scant relatively basophilic cytoplasm, while the latter were more mature, slightly larger cells, smaller than normal hepatocytes, with eosinophilic granular or clear cytoplasm and round nuclei.

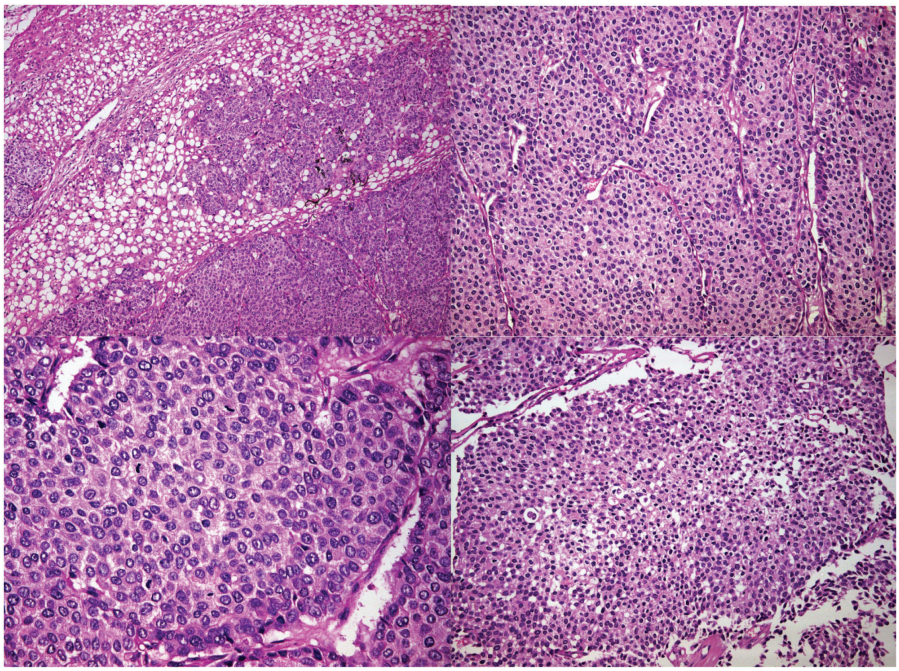

Figure1. *(a) Neoplastic cells infiltrating the adjacent non-alcoholic fatty liver parenchyma (H&E ×10), (b) Macrotrabecular arrangement of neoplastic cells (H&E ×20), (c) Fetal cell subtype could be divided into mitotically inactive (<2/10HPF) or active (>2/10HPF) areas; mitotically active area is associated with poorer prognosis (H&E ×40), (d) Embryonal cell subtype with more hyperchromatic and mildly pleomorphic cells is observed with a somewhat discohesive area. (H&E ×20).*

Both were arranged in trabeculae of six or more tumor cells, separated by thin fibrous septa. Between these aggregations of tumor cells, a diffuse network of thin-walled vessels with sinusoidal characteristics was observed while the bile duct network was absent. The mitotic rate was increased (~31 mitoses/10 High Power Fields ×40).

The immunohistochemical assessment of the tumor cells revealed positivity for AFP, Glypican-3, Glutamate synthetase, polyclonal Carcinoembryonic antigen, Cytokeratin (CK8/18), and Epithelial Specific Antigen/Ep-CAM (MOC-31), membranous and focally nuclear positivity for b-catenin, focal positivity for CK19 and vimentin and faintly focal positivity for Sal-like protein-4 (SALL-4) and Cluster Differentiation (CD99). The rest of the immunohistochemical assay (Hepatocyte/Hep-Par1, Arginase-1, caudal-related homebox-2, Thyroid Transcription Factor, CD56, Synaptophysin, Chromogranin, CK7, CD10, Androgen Receptors, Progesterone Receptors, Estrogen Receptors, Melan-A, SF1, and Inhibin-1) was negative (Figure 2). The cell proliferation rate of Ki-67 was high, at about 85%.

Concerning the prognostic markers, there was a positive expression of Cyclin D1 at approximately 80% of the tumor cells, while c-myc was negative.

All these clinical, morphological, and immunohistochemical findings lead us to the diagnosis of hepatoblastoma, macrotrabecular subtype. Nine months after the diagnosis, the patient deceased.

Discussion

Hepatoblastoma is a high-grade malignancy with complex pathogenesis; the stage and microenvironmental milieu at which primary hepatoblasts or highly proliferative undifferentiated multipotent hepatic progenitor cell undergo mutations that determine the differentiation pattern of the resulting tumor [6,7], giving rise to the corresponding histomorphology of epithelial phenotypes (less differentiated embryonal and differentiated fetal) and mesenchymal elements (mature fibrous tissue or hyaline cartilage) [8].

Macrotrabecular pattern is considered a subtype of epithelial hepatoblastoma; it consists of thick trabeculae (5-12 cells thick) that may be composed of fetal or embryonal hepatoblasts, pleomorphic cells, or large cells that resemble those of hepatocellular carcinoma [9] It is very rare, as it is accounted for only 3% of epithelial hepatoblastoma [9].

In contrast to pediatric hepatoblastoma, it is stated that adult hepatoblastoma has more histopathological similarities with hepatocellular carcinoma. Even more, macrotrabecular subtype of hepatoblastoma is very similar to hepatocellular carcinoma [10] due to the trabecular architecture of the latter and their differentiation is not only difficult but crucial for further therapeutic management, as adult hepatoblastoma is chemosensitive while hepatocellular carcinoma is not.

Some clinical features as underlying liver disease, patient age, and AFP serum levels could be helpful; metabolic disorders and cirrhosis favor hepatocellular carcinoma while age <5 years suggests hepatoblastoma. As for AFP levels, normal or mildly elevated number in any liver tumor with hepatocellular differentiation is not usual in hepatoblastoma, but this marker cannot be considered reliable. Other clues in favor of hepatoblastoma are the presence of other patterns of hepatoblastoma and its presentation

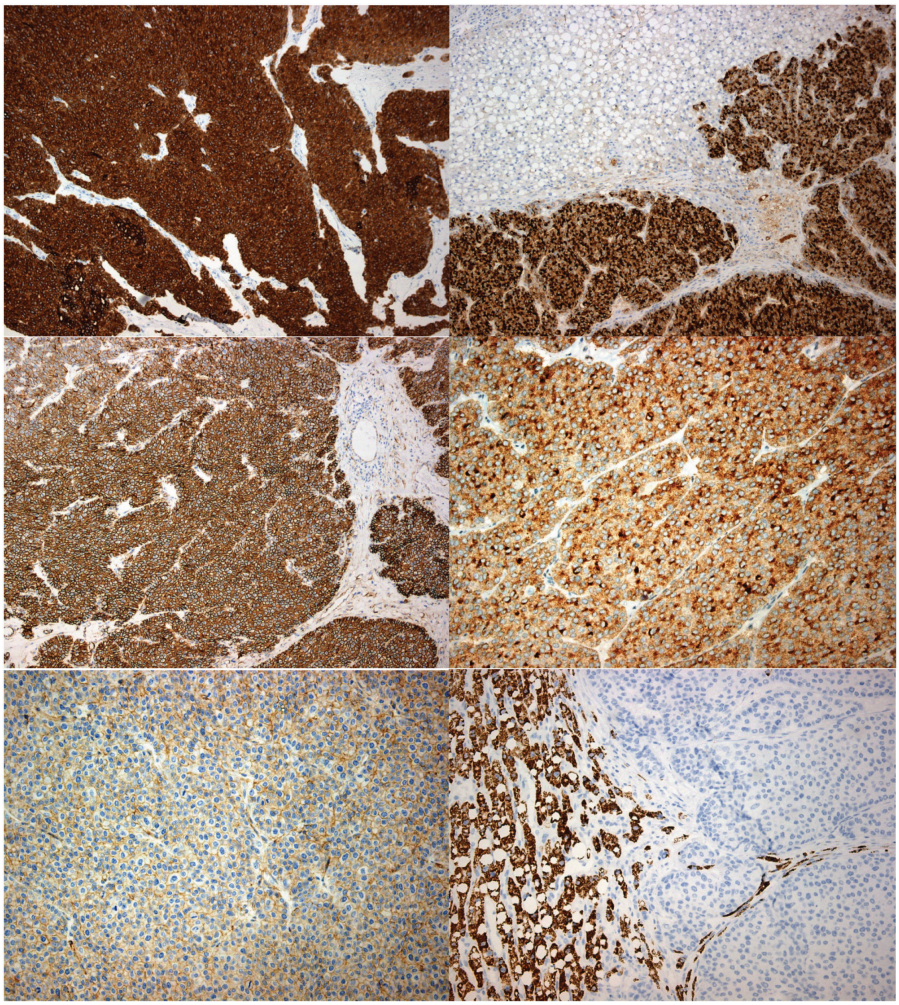

Figure 2. *(a) Strong diffuse positivity in CK8.18 (×10), (b) Diffuse positivity in AFP, while it is negative in the benign hepatocytes (×10), (c) Strong cytoplasmic staining in β-catenin (×10), (d) Fine either coarse granular staining of Glypican-3. According to WHO Classification of Digestive System Tumours (2019), fine granular staining is expressed in low-mitotic, well-differentiated component (×20), (e) Mild to medium cytoplasmic staining of CD99 (×10), (f) No staining of Hep Par-1 antibody in contrast to adjacent benign liver cells (×20).*

in a non-cirrhotic liver. Finally, no immunohistochemical marker is specific to differentiate hepatoblastoma from hepatocellular carcinoma [11].

In our case, high AFP serum levels and histomorphology of the tumor were the main keys that lead us to the diagnosis of hepatoblastoma. Also, it could be taken into consideration that positivity of MOC-31 argues against hepatocellular carcinoma, as this marker is widely used to differentiate hepatocelular carcinoma from hepatic metastases [12]. In addition, as adjacent benign liver parenchyma is characterized by simple steatosis without histologic liver injury or inflammation; changes indicative of non-alcoholic fatty liver, or non-alcoholic fatty liver disease without non-alcoholic steatohepatitis, this condition is not expected to develop cirrhosis or hepatocellular carcinoma [13,14].

In contrast to the treatment of pediatric hepatoblastoma, which is based on The International Childhood Liver Tumor Strategy Group [Société Internationale d'Oncologie Pédiatrique – Epithelial Liver Tumor Study Group (SIOPEL)] strategies, there is no standard evidence-based treatment for adult hepatoblastoma up to date [15]. Also, applying SIOPEL protocols in patients with adult hepatoblastoma, prognosis still remains poor. Despite the proposal of different treatments such as chemoembolization, radiofrequency therapy, and systemic chemotherapy, surgery remains the gold standard of treatment.

Conclusion

The difficulty in distinguishing macrotrabecular type adult hepatoblastoma from hepatocellular carcinoma could be overcome by the appropriate assessment of histomorphology, clinical, and laboratory findings. The extreme rarity of hepatoblastoma in adults makes it not commonly considered in the differential diagnosis of a liver mass, thus the diagnosis is established late with poorer prognosis than pediatric hepatoblastoma [16].

What is new?

Hepatoblastoma is a malignant tumor of the liver usually occurring in children, whereas it is very rare in adults. Although in our case the age, clinical, and laboratory findings suggested hepatocellular carcinoma, and the histological examination revealed a hepatoblastoma.

List of Abbreviations

AFP alpha Fetoprotein
CD Cluster Differentiation
CK Cytokeratin
MOC-31 Epithelial Specific Antigen/Ep-CAM

Funding

None.

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

Consent for publication

A written consent of the patient was taken.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	A 20-year old female
2	**Final diagnosis**	Hepatoblastoma
3	**Symptoms**	Palpable (10 cm) liver mass
4	**Medications**	-
5	**Clinical procedure**	Histopathological examination
6	**Specialty**	Pathology