**Two Cases of Hepatoblastoma in Adults**

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**ABSTRACT:** Adult hepatoblastoma is a rare tumor whose etiology and mechanisms of development are still incompletely understood. Imaging and biological tests such as AFP and liver enzymes are non-specific. Histologically, there are 2 histological variants: pure epithelial with 5 types (pure fetal, embryonal, small cell undifferentiated, cholangioblastic, and macrotubular), a mixed epithelial and a mesenchymal variant with or without a teratoid contingent. The main differential diagnosis concerns hepatocellular carcinoma. The treatment of hepatoblastoma in adults is not yet standardized and surgery remains the mainstay of treatment. In this report we aim to describe the clinical, pathological, and immunohistochemical features of this rare entity in adult patients and discuss the elements allowing its distinction from hepatocellular carcinoma (HCC).

**KEYWORDS:** Liver tumor, adult hepatoblastoma, pathology

**Introduction**

Hepatoblastoma (HB) is the most frequent liver tumor in children which accounts for 79% of pediatric malignant liver tumors but only 2% of all pediatric malignancies. The majority of cases are diagnosed within the first 3 years of life. However, Hepatoblastoma is an exceptional cause of primary malignant liver tumors in adults with a very poor prognosis and a high rate of mortality. Because of its rarity in adult patients, treatment for adult hepatoblastoma is not yet standardized as in children and surgery remains the mainstay of the treatment

In this report, we present 2 cases in young adult patients who consulted for abdominal pain.

**Case Report 1**

We report the case of a 26-year-old female patient with no previous history, who was admitted to the hospital because of a mass in the right hypochondrium. Abdominal MRI revealed a multiloculated cystic formation in segment VI of the liver, without intense contrast after injection with an Alpha Foeta Protein level of 2275 IU/ml. Liver function test and lactate dehydrogenase were within normal limits and hepatitis (B and C) tests were negative.

The patient underwent an S5-S6 bi-segmentectomy associated with cholecystectomy and hepatic pedicle curage.

The macroscopic examination showed several confluent nodules forming a single mass measuring 8, 7 × 6 × 5 cm in size with a crisp texture. The surface of the liver was smooth without obvious disruption. The cut surface showed a yellow lobulated lesion with areas of necrosis and hemorrhage.

Microscopic examination showed a non-cirrhotic liver parenchyma which is the site of an epithelial proliferation with a double component. The first is formed of small and uniform cells arranged in thin trabeculae, the cytoplasm was either eosinophilic or clear with an appearance of light and dark pattern at low magnification. In the second pattern, the tumor cells were arranged in glandular, acinar or pseudorosettes structures. Mitotic activity was low in the epithelial component but high in the mesenchymal component. Tumor cells, resembling blastemal cells, showed a dark and scant cytoplasm with large nuclei. Immunostaining showed positive labeling of the cells with anti-hepatocyte and anti-glypican3 antibodies in both components. Tumor cells were negative for chromogranine and synaptophysin (Figure 1).

The final diagnosis was mixed fetal and embryonic epithelial hepatoblastoma.

The patient was referred to the oncology department for chemotherapy.

**Case Report 2**

The second patient was an alcoholic 50-year-old male, who presented to the emergency department with a complaint of acute abdominal pain. Physical examination revealed severe abdominal distension. Abdominal computed tomography (CT) showed a large lobulated solid mass involving the entire liver with intra-abdominal fluid accumulation. A ruptured hepatic tumor with massive internal bleeding was suspected. At the time of diagnosis, routine blood investigations including liver function tests were all within normal ranges. Screening for viral markers was negative. The baseline serum alpha fetoprotein (AFP) was elevated (6386 ng/ml). They had urgently taken him to the operating room where an exploratory laparotomy was performed and good hemostasis was obtained after blood transfusion.
Clinical Pathology

We received pre-operative fragmented liver biopsies. Histopathological examination revealed that the tumor is composed exclusively of immature hepatocytic elements and made up of mesenchymal and epithelial cells. The epithelial component is characterized by a fetal and embryonal pattern. The tumor cells were grouped in nests, islands, and broad trabeculae with a small round nucleus and finely granular eosinophilic cytoplasm. Some areas showed glandular configuration, acini and rosette formation, with brisk mitotic activity. The mesenchymal component comprised spindle oval cells with minimal cytoplasm, myxoid degeneration and necrosis. There was no evidence of extramedullary hematopoiesis or lymphovascular invasion.

Immunohistochemical stainings showed that the tumor cells were positive for synaptophysin and chromogranin A, but negative for panCk, Ck7, Ck20, and PLAP. Scattered cells showed positive staining of EMA, β-catenin staining exhibited a mixed nuclear and cytoplasmic pattern of the tumor cells (Figure 2). These pathology results were consistent with the diagnosis of a mixed hepatoblastoma. Following laparotomy, the patient was treated with adjuvant chemotherapy and surgical resection was planned.

Discussion
In children, HB is the most frequent primary malignant liver neoplasm with a significant increase in incidence per year. It occurs typically in patients under 5 years (91% of liver malignancies). Only 5% of HBs are in patients aged >4 years. The average age at diagnosis ranges from 12 to 21 months.4,5

The etiology and mechanisms of hepatoblastoma are still unclear. However, several risk factors have been described such as prematurity, very low birth weight (<1500 g), maternal and paternal preconceptional and gestational tobacco smoking.6

Reports of children hepatoblastoma cases revealed that this pathology can be associated with genetic syndromes specifically Beckwith-Wiedemann syndrome, hemihypertrophy, Prader-Willi, Simpson-Golabi-Behmel, Aicardi (X-linked mutation), trisomy 18 and Familial adenomatous polyposis.7

In Adults, hepatoblastoma is an uncommon liver tumor. The first case of this tumor in a young man was reported in 1958. Only 69 cases of this pathology have been recognized in the literature up to December 2018.

A review of 63 cases of hepatoblastoma in adults by Celotti et al published in 2016, revealed that the age of the patients reported ranged from 18 to 84, with a median age of 42 years. The ratio male: female was 1. Only in 49 articles sex was specified: 24 patients males and 25 females.8

A subsequent study published in 2019 added 6 new cases reported in the literature from 2016 to December 2018.

Different investigations of genetic abnormalities in HB revealed different alterations such as alteration of the wnt/β-catenin signaling pathway including mutations in CTNNB1, AXIN1, APC and, p53.9 The insulin growth
factor 2 (IGF2) pathway is activated by genetic or epigenetic events such as allelic deletion of chromosome 11p15.5. Upregulation of cell-cycle pathway and loss of checkpoint contrôle (including PLK1-CDKN2A-CDKN1B), microsatellite instability and many other molecular abnormalities were also found. Moreover, these tumors show few chromosomal abnormalities.

The most common are trisomies of chromosomes 2, 8, and 20, the gain of chromosome 22 and rearrangements or translocations affecting chromosomes 1q, 2, and 4q.

The revealing sign of hepatoblastoma is usually the right upper quadrant abdominal pain or the presence of abdominal mass. Other clinical symptoms included hemoperitoneum due to rupture of the tumor, massive gastrointestinal bleeding, fever, vomiting, loss of energy, norexia, and loss of weight. HB can be well tolerated by patients and has few symptoms.

In the literature, laboratory studies including blood count, liver function test, lactate dehydrogenase and, serological hepatitis revealed nonspecific results. Alpha-fetoprotein (AFP) with hepatoblastoma is usually increased, however some patients can have normal or low AFP level like hepatocellular carcinoma.

Hepatoblastomas are classified by the International Pediatric liver Tumors Consensus Classification as either epithelial or mixed epithelial and mesenchymal. (Table 1) It is based on the histological classification of HB originally proposed by Ishak and Glunz in 1967.

The radiological investigations, including abdominal ultrasonography, axial tomography and magnetic resonance imaging, may show single or multiple lesions. Tumors may appear as a large nodular mass surrounded by a fine fibrous capsule, pseudocapsule or with indistinct margins. Calcifications, hemorrhage and necrosis were noted in some cases.

Generally, imaging is not useful for the diagnosis of hepatoblastoma because there are no specific radiological signs of hepatoblastoma and different types of liver tumor, such as HCC, presented the same characteristics. However imaging is particularly useful to evaluate pulmonary metastasis and lymph node status.

Hepatocellular carcinoma is the main differential diagnosis. The differentiation between these 2 entities may be difficult because of the lack of particular clinical signs and radiological features. Histological study plays a key role in this distinction. The main histological criteria to distinguish HB from HCC are the presence of "light and dark" pattern, extramedullary hematopoiesis and mesenchymal elements.

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Clinical Pathology

Table 1. Hepatoblastomas classification by the International Pediatric liver Tumors Consensus Classification.

| Classification                        | Description                                                                 |
|---------------------------------------|-----------------------------------------------------------------------------|
| Epithelial                            |                                                                            |
| Fetal                                 |                                                                            |
| Fetal with low mitotic activity        |                                                                            |
| Fetal mitotically active               |                                                                            |
| Pleomorphic                            |                                                                            |
| Embryonal                             |                                                                            |
| Small cell undifferentiated           |                                                                            |
| SMARC B1 (INI1)-negative              |                                                                            |
| SMARC B1 (INI1)-positive               |                                                                            |
| Cholangioblastic                      |                                                                            |
| Macrotrabecular                        |                                                                            |
| Mixed epithelial                      |                                                                            |
| Mixed epithelial and mesenchymal      |                                                                            |
| Without teratoid features             |                                                                            |
| With teratoid features                |                                                                            |

**Embryonal pattern:** It is less differentiated than the fetal type contingent and resembles the developing embryonic liver. Cells are small, elongated and arranged in solid nests, ribbons, acinar or papillary structures, or pseudorosettes. Cytoplasm is dark, scant, and amphiphilic without glycogen and lipid content. The nucleus is round to oval, hyperchromatic and contains a large nucleolus. The mitoses are frequent.

Fetal and embryonal epithelial patterns are usually associated.1-16

Immunohistochemistry, tumor cells show AFP and nuclear b-cat positivity. GS is variable. GPC3 is also variable, it may be absent or show strong, coarse, diffuse cytoplasmic staining. Ki67 is high.

**Small cell undifferentiated HB:** is characterized by solid sheets of small and poorly cohesive cells, with scant cytoplasm and hyperchromatic nuclei similar to the neuroblastoma cells. It may be associated with a fetal or an embryonal pattern. INI 1 can be positive or negative in the SCUD pattern with a better prognosis for SMARC B1(INI 1)-positive.

Immunohistochemically, the SCUD pattern shows strong and diffuse nuclear b-catenin stain; it expresses also pancytokeratin, cytokeratin 19, and vimentin; in contrast it is negative for Hep Par 1, AFP, GS, and GPC3.

**The cholangioblastic pattern:** shows small ductal structures or sheets formed by cuboidal cells.

Tumor cells of cholangioblastic pattern show nuclear b-catenin stain, which is not seen in the reactive ductular population. These cells are also positive for CK7, CK19 but negative for GS and GPC3.

**The macrotrabecular pattern:** is defined by the presence of trabeculae with more than 5 cells thickness. The cells can show fetal or embryonal morphology.

The Immunostains show strong nuclear b-catenin stain. Mixed epithelial and mesenchymal hepatoblastoma with teratoid features show variable result depending on the components.1–17

Due to the rarity of hepatoblastoma in adults, there is no standardized management of adult HB. Surgery is the mainstay of treatment. It aims for complete tumor resection. Although, some tumors are so big or extensive and cannot be completely removed3,15 Liver transplantation can be considered in these cases.4 Surgery can be combined with chemotherapy as adopted in children, Cisplatin is the most commonly used

**Mixed epithelial and mesenchymal hepatoblastoma**

It is characterized by the association of mesenchymal and epithelial elements. The mesenchymal components may be composed of fibrous, osteoid and cartilage tissue. Mixed hepatoblastoma may present teratoid features composed of the endodermal (glandular, endocrinoid), neuroectodermal (glial elements, neuronal cells) or complex mesenchymal tissues (striated muscle).

It express a nuclear b-catenin stain. Mixed epithelial and mesenchymal hepatoblastoma with teratoid features show variable result depending on the components.1–17

Histologically, the tumor consists of irregular lobules delineated by septa of varying thicknesses. These septa are composed of mature collagenous fibers, and contain usually venous vessels and lymphatics.16

It can be subdivided into:

**Fetal epithelial pattern:** It has an appearance comparable to that of the fetal liver. Cells are usually polyhedral, smaller than the normal parenchymal cells and show some variation in size. The cytoplasm is granular and acidophilic, they may contain glycogen or lipid content, which gives them a characteristic bicolor appearance (light and dark pattern in low magnification). These cells are usually arranged in thin trabeculae and rarely in an acinar arrangement. Extramedullary hematopoiesis is seen. The well-differentiated fetal hepatoblastoma has a low mitotic activity.

Immunohistochemically, tumor cells are strongly positive for glutamine synthetase (GS), and show finely granular staining with glypican 3 (GPC3).b-catenin (b-cat) is frequently membranous and even cytoplasmic, with rare nuclear staining. Hep-Par1 and AFP are also positive.

The “crowded” or mitotically active fetal HB has the fetal aspects described above. It is specifically defined by a mitotic index of more than 2 mitoses per 10 fields at high magnification. The pleomorphic fetal is defined by nuclear pleomorphism with anisokaryosis and multinucleated cells.1–9

The Immunostains show strong positivity for GPC3 in a diffuse, coarse, cytoplasmic staining pattern and GS. Many positive nuclei for b-cat are seen. Hep-Par1 and AFP are positive.

The “pleomorphic” fetal hepatoblastoma shows a greater degree of nuclear pleomorphism with anisokaryosis and multinucleation, and less well-defined trabeculae. The mitotic activity is considerably increased. Immunohistochemically, tumor cells are strongly positive for glutamine synthetase (GS), and show finely granular staining with glypican 3 (GPC3).b-catenin (b-cat) is frequently membranous and even cytoplasmic, with rare nuclear staining. Hep-Par1 and AFP are also positive.

The “crowded” fetal hepatoblastoma has the fetal aspects described above, but with higher mitotic activity. Immunohistochemically, tumor cells are strongly positive for glutamine synthetase (GS), and show finely granular staining with glypican 3 (GPC3).b-catenin (b-cat) is frequently membranous and even cytoplasmic, with rare nuclear staining. Hep-Par1 and AFP are also positive.

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chemotherapeutic agent.\textsuperscript{15} Preoperative chemotherapy can be used to reduce the volume of unresectable tumors that are too big for conventional surgery.\textsuperscript{2,16}

**Conclusion**

Adult hepatoblastoma is a rare entity with a poor prognosis, whose diagnosis is based on histology given the non-specific clinical, radiological and biological picture. The optimal treatment remains to be defined due to the limited data available.

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Not applicable.

**Author Contributions**

IE and EH analyzed and interpreted the patient data and wrote the manuscript. IE made the figures. IE performed the histological examination. BS and EB proposed the study, supervised IE and revised the manuscript. All authors read and approved the final manuscript.

**Ethical Approval**

Not applicable.

**Consent for Publication**

Written consent has been obtained from the patient and the patient’s family for the publication of this case report.

**Guarantor**

Ihssan Elouarith

**REFERENCES**

1. Taque S, Morcrette G, Brugières L, Franchi-Abella S, Branchereau S, Frenneau I. Hépatoblastome chez l'enfant. *Pédiatrie – Maladies Infectieuses*. 2020-09-01;40:1-10.
2. Pila-Perez R, Sauvith-Monterrosa JL, Rosales-Torres P, Pila-Peláez R, Artola-Gonzalez JA. A case of adult hepatoblastoma. *Rev. colomb Gastroenterol*. 2020;35:220-225.
3. Rougemont A-L, McLin VA, Toso C, Wildhaber BE. Adult hepatoblastoma: learning from children. *J Hepatol*. 2012;56:1392-1403.
4. Allan BJ, Parihk PP, Diaz S, Perez EA, Neville HL, Sola JE. Predictors of survival and incidence of hepatoblastoma in the paediatric population. *HPB*. 2013;15:741-746.
5. Zhang Y, Zhang WL, Huang DS, Hong L, Wang YZ, Zhu X, et al. Clinical efficacy and prognosis factors for advanced hepatoblastoma in children: a 6-year retrospective study, Asian pac. *J Cancer Prev*. 2013;14:4583-4589.
6. von Schweinitz D. Hepatoblastoma: recent developments in research and treatment. *Semin Pediatr Surg*. 2012;21:21-30.
7. Perilongo G, Shafford EA. Liver tumours. *Eur J Cancer*. 1999;35:953-958.
8. Celotti A, D'Amico G, Ceresoli M, et al. Hepatoblastoma of the adult: a systematic review of the literature. *Surg Oncol*. 2016;25:339-347.
9. World Health Organization. *WHO Classification of Tumors of the Digestive*. 5th ed. IARC Press; 2019.
10. Fiaschetti V, Fiori R, Gaspari E, Crusco S, Simonetti G. Mixed hepatoblastoma in a young male adult: a case report and literature review. *Case Rep Med*. 2010;2010:1-5.
11. Zheng MH, Zhang L, Gu DN, Shi HQ, Zeng QQ, Chen YM. Hepatoblastoma in adult: review of the literature. *J Clin Med Res*. 2009;1:13-16.
12. Bandia MA. Genetic alterations in hepatoblastoma and hepatocellular carcinoma: common and distinctive aspects. *Med Pediatr Oncol*. 2002;39:530-535.
13. Celotti A, Baiocchi GL, Ceresoli M, Bartoli M, Ulinici S, Portolani N. Hepatoblastoma of the adult with pericardial metastasis: a case report. *Int J Surg Case Rep*. 2016;20:80-83.
14. Xu SY, Tao L, Liu H. Adult hepatoblastoma: systemic review of the English literature. *Dig Surg*. 2012;29:323-330.
15. Zhong S, Zhao Y, Fan C. Hepatoblastoma with pure fetal epithelial differentiation in a 10-year-old boy: a rare case report and review of the literature. *Medicine*. 2018;97:e1627.
16. Lihak KG, Glunz PR. Hepatoblastoma and hepatocarcinoma in infancy and childhood. Report of 47 cases. *Cancer*. 1967;20:396-422.
17. Ranganathan S, Lopez-Terrada D, Alaggio R. Hepatoblastoma and pediatric hepatocellular carcinoma: an update. *Pediatr Dev Pathol*. 2020;23:79-95.