Atypical Hepatocellular Neoplasm With Peliosis in Cirrhotic Liver Versus Hepatocellular Carcinoma

A Diagnostic Trap

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Abstract: Atypical hepatocellular neoplasm (AHN) is an adenoma-like hepatic tumor that even occurs in noncirrhotic liver of males (any age) or females ≥50 years old, or associates focal atypical features.

INTRODUCTION

Hepatic or hepatocellular adenoma (HA), also known as benign hepatoma, is a rare benign tumor that represents <3% of all primary tumors of the liver and occurs in 95% of the cases in women younger than 45 years taking oral contraceptives; the annual incidence is 3 to 4 cases/100,000 females. The first case of HA was described by Franco et al in 1952 as an encapsulated liver tumor without bile ducts, whereas, in 1973, Bana et al evolved the possibility of association between HA and contraceptive pills consumption. Later, it was proved that cessation of consumption of steroid hormone-based pills could lead to spontaneous tumor regression.

HAs are considered tumors of noncirrhotic liver that are unusual in males (any age) and women <50 and >15 years old, and their differential diagnosis is very difficult. Except the patient’s age and gender, HAs in the setting of cirrhosis can be diagnosed in only those cases that really satisfy all the diagnostic criteria very stringently (Table 1). Moreover, in adults (males at any age and females >50 years) and also in cases with focal atypical features (Table 1) the diagnosis of atypical hepatocellular neoplasm (AHN) is recommended.

In this article, we present 2 cases that were first diagnosed as HAs with associated peliosis, developed in the hepatitis B-related cirrhotic liver of 2 elderly patients, with high risk of bleeding. Further careful examination led to modified diagnosis: one of the cases was classified as AHNs and the other one was considered well-differentiated hepatocellular carcinoma (HCC). Besides the clinicopathologic characteristics of the cases, the criteria of differential diagnosis of HA versus AHN and HCC were presented with illustrative pictures. Consent of the patients was obtained for surgical intervention and publication of these cases.

PRESENTATION OF CASES

Case 1
An 83-year-old nonalcoholic female, with 6 months history of lithiasic cholecystitis, was admitted to the hospital with severe right upper quadrant and epigastric pain, nausea, vomiting, and scleral jaundice. Emergent laparoscopic cholecystectomy was decided. Before surgical intervention, ultrason sound examination was performed and a hepatic hemangioma of the V, VI, and VII segments of the liver was suspected.

Her past medical history included nonoperated acute pancreatitis (10 years before) and hepatitis B-related Lennec’s atrophic cirrhosis (diagnosed 6 years before; at the moment, in compensated status). Five years ago, she was also diagnosed with a right breast neuroendocrine invasive tumor in pT2N0 stage; right mastectomy was performed, without any postoperative oncologic therapy. No recurrences or metastases were
| Parameter                  | Hepatocellular Adenoma                                                                 | Atypical Hepatocellular Neoplasm                                                                 | Hepatocellular Carcinoma                                                                 | Focal Nodular Hyperplasia With Large Cell Change                                                                 | Dysplastic Nodule (Adenomatous Hyperplasia With Large Cells)                                                                 | Macro-Regenerative Nodule                                                                 | Intrahepatic Bile Duct Adenoma             | Intrahepatic Cholangiocarcinoma |
|---------------------------|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|---------------------------------------|----------------------------------------|
| Epidemiology              | Usually females (>15 years and <50 years old), taking steroid hormones (90–95%)        | Usually males, any age or females outside the 15- to 50-year age group                           | Usually young females (>80%)                                                             | Usually males                                                                                                   | Usually males                                                                                                                 | Both genders                                                                                   | Both genders                          |                                        |
| Steroid hormones          | Usually yes                                                                           | Usually not normal or minimally elevated                                                      | NS                                                                                      | NS                                                                                                               | NS                                                                                                                            | NS                                                                                                          | NS                                     |                                        |
| Associated cirrhosis      | Usually not normal or minimally elevated                                              | Usually not normal or minimally elevated                                                      | NS                                                                                      | NS                                                                                                               | NS                                                                                                                            | NS                                                                                                          | NS                                     |                                        |
| Serum αFP                 | Usually one subcapsular encapsulated nodule >4 cm                                     | Usually one nodule with multinodular aspect on cut-section                                      | Solitary, nodular, or diffuse tumor, mostly nonencapsulated nodules with infiltrative edges | Usually one nonencapsulated nodule with a central fibrosis, but multiple nodules can be present                  | Multiple 1–3 cm well-defined nonencapsulated nodules                                                                     | Usually single subcapsular nodules <2 cm                                                      |                                        |                                        |
| Macrosopy                 | Very rare >10 nodules—“adeno-matosis”                                                 |                                                                                                 |                                                                                          |                                                                                                                  |                                                                                                                                |                                                                                                                             |                                        |                                        |
| Histology                 | Encapsulated tumor composed by one-to-two hepatocyte-like cells thick plates, with solid, trabecular, and inconstant acinar/pseudoglandular pattern | Hepatocellular adenoma-like histological aspect, with intact reticulin framework and usually acinar pattern | Proliferation of >3 hepatocyte-like cells thick, with macrotrabecular, acinar, solid, or scirrhous pattern | Nonencapsulated tumor, with a central scar and multinodular pattern, composed by 1–3 proliferated hepatocytes thick, without nuclear atypia, without mitoses | Nonencapsulated nodules composed by hepatocyte-like cells with abundant cytoplasm, large nuclei, hyperchromasia and prominent nucleoli, with normal nuclear-to-cytoplasm ratio, and infrequent multinucleated cells, without mitoses | Nonencapsulated nodule composed by tubular structures lined by columnar epithelium, sometimes with clear cytoplasm, without cytologic atypia, without mitoses |                                        |                                        |
| Eosinophilic clear cytoplasm, usually with bile pigment (slow growing) | Without mitotic activity, without vascular invasion                                      | Eosinophilic or clear cytoplasm, without bile pigment (rapid growing)                          | Hypovascular fibrous stroma with thick-walled arteries                                    | Intact portal spaces, intact reticulin framework                                                               | Thick fibrous septa                                                                                                           | Fibrous stroma, more prominent in the central part than in the periphery, intact reticulin framework |                                        |                                        |
| No or occasional cytological atypia, without mitoses | With inconstant focal small cell changes and abnormal hepatocyte trabeculae            | Large atypical nuclei and prominent nucleoli, with abnormal nuclear-to-cytoplasm ratio or small cell changes, and mitoses | Significant ductular proliferation surrounded by lymphocytes, no portal spaces, very few Kupffer cells, intact reticulin framework | Well-vascularized fibrous stroma with unpaired artery                                                      |                                                                                                                                |                                                                                                                             |                                        |                                        |
| Very well-vascularized scant stroma with “naked arterioles” | Usually with chromosomal abnormalities                                                 | Hypervascular scant stroma with “naked arterioles” and vascular invasion                       | Focal/peripheral bile ducts proliferation, intact portal spaces, intact reticulin framework |                                                                                                                  |                                                                                                                                |                                                                                                                             |                                        |                                        |

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| Parameter | Hepatocellular Adenoma | Atypical Hepatocellular Neoplasm | Hepatocellular Carcinoma | Focal Nodular Hyperplasia | Dysplastic Nodule With Large Cell Change | Macro-Regenerative Nodule (Adenomatous Hyperplasia With Large Cells) | Intrahepatic Bile Duct Adenoma | Intrahepatic Cholangiocarcinoma |
|-----------|------------------------|---------------------------------|-------------------------|-------------------------|----------------------------------------|-------------------------------------------------|-------------------|------------------------|
| No bile ductules, no portal spaces, no Kupfer cells, intact reticulin framework | No ductular proliferation, no portal spaces, no Kupfer cells, disintegrated reticulin framework with thick fibrous bands | With chromosomal abnormalities | Usually not | Usually not | Usually not | Usually not | Usually not | Usually not |
| No genomic instability | Associated peliosis hepatis | Usually yes, sometimes with postinfarcted scar | NS | Usually not | Usually not | Usually not | Usually not | Usually not | Usually not |
| Keratin AE1/AE3, HepPar1 | Polyclonal CEA — inconstant | Keratin AE1/AE3, HepPar1 | Polyclonal CEA, HEPPar 1, p53, Ki-67 — inconstant | Polyplonal CEA, HEPPar 1, p53, Ki-67 — inconstant | Keratin AE1/AE3, HepPar1 | Keratin AE1/AE3, HepPar1 | Keratin AE1/AE3, 7, polyclonal CEA, p53 | Keratin AE1/AE3, 7, polyclonal CEA, p53 |
| Keratin AE1/AE3, HepPar1 | Polyplonal CEA, HEPPar 1, p53, Ki-67 — inconstant | Keratin AE1/AE3, HepPar1 | Keratin AE1/AE3, HepPar1 | Keratin AE1/AE3, HepPar1 | Keratin AE1/AE3, HepPar1 | Keratin AE1/AE3, HepPar1 | Keratin AE1/AE3, 7, polyclonal CEA, p53 | Keratin AE1/AE3, 7, polyclonal CEA, p53 |
| Keratin AE1/AE3, HepPar1 | Polyplonal CEA, HEPPar 1, p53, Ki-67 — inconstant | Keratin AE1/AE3, HepPar1 | Keratin AE1/AE3, HepPar1 | Keratin AE1/AE3, HepPar1 | Keratin AE1/AE3, HepPar1 | Keratin AE1/AE3, HepPar1 | Keratin AE1/AE3, 7, polyclonal CEA, p53 | Keratin AE1/AE3, 7, polyclonal CEA, p53 |
| Polyplonal CEA, HEPPar 1, p53, Ki-67 — inconstant | Keratin 7 positive ductular reaction | CD34—positive sinusoids | Keratin 7 positive ductular reaction | CD34—positive sinusoids | Keratin 7 positive ductular reaction | CD34—positive sinusoids | Keratin 7 positive ductular reaction | Keratin 7 positive ductular reaction |
| Keratin 7, 20, αFP, vimentin, monoclonal CEA, Ki-67, glypican inconstant | Keratin 7, 19, 20, αFP, vimentin, monoclonal CEA | Keratin 7, 19, 20, αFP, vimentin, monoclonal CEA | Keratin 20, αFP, Ki-67 | Keratin 20, αFP, Ki-67 | Keratin 20, αFP, Ki-67 | Keratin 20, αFP, Ki-67 | Keratin 20, αFP, Ki-67 | Keratin 20, αFP, Ki-67 |

αFP = alpha fetoprotein, CA = carbohydrate antigen, CD = cluster of differentiation, CEA = carcinoembryonic antigen, EMA = epithelial membrane antigen, HepPar = hepatocyte paraffin, IHC = immunohistochemistry, NS = nonspecific.
suspected. The gynecologic examination revealed no modifications.

At the current admission, blood tests did not show significant disorders except slight anemia (hemoglobin 10.40 g/dL and hematocrit 29.90%), lymphopenia (18.50%), and slight elevated aspartate aminotransferase and alanine transaminase (AST 52.00 U/L, ALT 83.00 U/L).

During laparoscopic surgery, exploration of the peritoneal cavity revealed hemoperitoneum. Laparotomy was performed and the distended gallbladder was removed. The peritoneal hemorrhage occurred as a result of rupture of a 75-mm diameter nodular tumor that was relatively well defined and involved the segments 5, 6, and 7 of the liver.

Gross examination of the surgical specimen showed a 75 mm × 70 mm × 55 mm encapsulated nodular tumor, with a 25 × 20 ruptured bleeding area. On cut section, the gray-colored tumor had a soft consistency and presented multiple hemorrhagic areas (Figure 1). The liver parenchyma adjacent to the tumor capsule had a nodular aspect and hard consistency. Histopathological examination revealed that the tumor was composed by closely packed hepatocytes delineated by the liver parenchyma through a connective capsule. The tumor cells, which displayed a solid architecture, were arranged in one-to-two closely packed rows, presented irregular cell boundaries, and a rich cytoplasm. Among the hepatocytes, several CD34-positive sinusoidal spaces intermingled with randomly distributed CD34-negative large blood-filled spaces and cysts surrounded by hepatocytes, suggestive for intratumor peliosis, were noted (Figure 2). At high power view, predominately clear cell cytoplasm was noted. Nuclear-to-cytoplasmic ratio was normal, no mitotic figures or nuclear polymorphism was seen. The tumor cells were marked by AE1/AE3 keratin and were negative for keratin 7, α-fetoprotein, monoclonal carcinoembryonic antigen (CEA), and p53, with a Ki67 index < 5%. The cytoplasm of the hepatocytes was not modified. No keratin 7 positive-biliary channels either portal spaces were present in the tumor parenchyma; the reticulin framework examined with reticulin stain was intact (Figure 2). The surrounding hepatic parenchyma showed a pseudolobular architecture; the pseudonodules of hepatocytes were surrounded by thin fibrous septa that incorporated pseudobiliary channels.

Based on the above findings, the initial diagnosis was HA with clear cell features and peliosis. Based on the patient’s age (female >50 years old) and occurrence of the tumor in the setting of cirrhosis (Table 1), the final diagnosis was AHN with peliosis. The HCC was excluded based on identification of one-to-two closely packed rows of proliferated hepatocytes, normal nuclear-to-cyttoplasmic ratio, low Ki67 index, and intact reticulin framework. The gallbladder examination confirmed the chronic cholecystitis. The patient was discharged after 1 week of hospitalization and is free of any complaints 6 months after surgery, without any additional therapy.

Case 2

A 66-year-old nonalcoholic male was admitted at the hospital with severe diffuse abdominal pain. His past medical history included primary hypertension and chronic B hepatitis, without Delta virus. Hepatitis was diagnosed 20 years before and was not treated with any drugs, except hepatoprotective pills. Two years ago, hepatitis-related Laennec atrophic cirrhosis was diagnosed. At the current admission, with no therapy, there were no signs of decompensated cirrhosis.

Physical examination did not reveal significant disorders, except a slight abdominal wall contraction. Ultrasound examination showed a 35 mm solid hepatic nodule in the sixth liver segment. Blood tests did not show significant disorders except slight anemia (hemoglobin 12.00 g/dL and hematocrit 35.20%), and lymphocytosis (46.00%). Transaminases were within normal limits (AST 25.00 U/L, ALT 22.00 U/L) as well as total bilirubin (0.40 mg/dL).

FIGURE 1. Gross findings of hepatic tumors from authors’ collection. (A and B) Atypical hepatocellular neoplasm—case 1; (C) encapsulated hepatocellular carcinoma—case 2; (D) multifocal hepatocellular carcinoma; (E) cholangiocarcinoma.
Based on these examinations, laparotomy was decided, and the sixth segment of the liver that embedded a well-defined encapsulated tumor was removed.

Gross examination of the surgical specimen revealed a 35 mm x 30 mm x 38 mm round encapsulated tumor, surrounded by hepatic parenchyma. On cut section, the tumor had a multinodular solid aspect, was green-yellow in color, soft in consistency, and presented multiple small hemorrhagic areas (Figure 1). The liver parenchyma adjacent to the connective capsule had a hard consistency and nodular aspect.

Under microscope, the encapsulated tumor was shown to be composed by multiple nodules separated by connective bands. Within the nodules, hepatocyte-like cells that displayed tubular or glandular-like, acinar and solid-trabecular...
arrangement of the tumor cells with clear component was noted. No atypical nuclei were identified; the reticulin framework was disintegrated (Figure 2). The tumor stroma was well vascularized, without ductular reaction or inflammatory cells. The hepatic parenchyma that was located adjacent to the connective capsule presented a pseudolobular architecture that was suggestive for cirrhosis, without signs of fatty change. The immunoprofile of the tumor cells was similar to Case 1.

Based on the microscopic aspect, the initial diagnosis was HA with mixed components, including trabecular and acinar structures. Based on the patient’s gender (elderly male), the multinodular aspect, 3 hepatocyte-like cells thick plates, many pseudoacini, disintegrated reticulin framework (Figure 2) and associated cirrhosis, the final diagnosis was well-differentiated HCC with peliosis (Table 1). The patient was discharged 9 days after surgery; there were no complaints 7 months after surgery.

DISCUSSION

HAs and adenoma-like tumors such as AHNs are incidentally discovered during computed-tomography, ultrasound, or magnetic resonance imaging (MRI) examinations. In HAs larger than 70 mm in diameter, spontaneous rupture, intraperitoneal bleeding, and even malignant transformation in HCC can occur, especially in males. Despite their apparently benign morphology, AHNs can recur and metastasize and it is likely that malignization of HA is rather an incorrect diagnosed AHNs. To prevent bleeding and/or consequences of malignant behavior, surgical excision of adenomatous lesions larger than 5 cm is recommended in females, and in males, removal of any tumor nodules, respectively.

In our first case, the risk factors for rupture and/or bleeding in a cirrhotic liver was the diameter that was higher than 70 mm, but the large peliotic areas can also indicate a high risk for bleeding and during ultrasound examination the tumor can be misconstrued as hemangiomas, such as in this case. Microscopically, in contrast to hemangiomas, the peliotic areas do not display endothelial-lined walls. Although HAs of the left hepatic lobe are more predisposed to rupture, in this case, the spontaneous bleeding occurred in a tumor that involved the fifth, sixth, and seventh segments of the right-inferior part of the liver.

FIGURE 4. Microscopic and immunohistochemical features of nontumor lesions of the liver that should be differentiated from hepatic adenomas and adenoma-like tumors.
Based on genetic and pathologic features, 4 major subtypes of HA are known, with specific histologic features and clinical behavior: inflammatory type (type 1 ~40–55% of the cases), hepatocyte nuclear factor (HNF-1α)-inactivated (type 2 ~15–50%) HA, β-catenin-mutated HA (type 3 ~10–18%), and unclassified HA (type 4 ~10–30%). Type 1 HA occurs in patients with a median age of 45 years and is characterized by: 4 to 5 cm nodules composed by proliferation of hepatocyte-like cells, a rich inflammatory stroma with ductular reaction, marked sinusoidal dilatation, and thick-walled arteries. In males with alcoholic cirrhosis, a serum amyloid-A positive inflammatory HA was recently described. Type 2 HA is usually asymptomatic and occurs almost exclusively in women below 45 years, about 90% of them having a history of contraceptives use. Microscopically, the nodules with a median diameter of 4 cm are composed by hepatocyte-like cells with excessive lipid accumulation in their cytoplasm and can occur on the background of a steatotic liver. The third type occurs more frequently in young males, is usually associated with male hormones consumption, and the diameter is larger than 15 cm. Microscopically, it is characterized by proliferation of hepatocyte-like cells that can present nuclear atypia and pseudocinar structures. Type 4 HA is more frequent in females that can present a history of contraceptives use, the diameter is around 4 cm, can be unique or multiple, and occurs in patients younger than 45 years.

The clinicopathologic characteristics of the first case presented in this article suggested a type 2 HA, an HNF 1α-mutated subtype, but its occurrence in an 83-year-old female and development in the background of hepatitis B-related liver cirrhosis indicated an AHN, based on the criteria synthesized in Table 1. In the second case, which occurred in a 66-year-old male, the pseudocinar structures suggested a type 3 HA, respectively a β-catenin-mutated HA. However, its occurrence in a male with liver cirrhosis and disintegrated reticulum framework asserted for HCC.

Besides HA, AHNs, and HCC, differential diagnosis of adenoma-like hepatic tumors that occurs in liver cirrhosis should also taken into account other primary hepatic lesions such as focal nodular hyperplasia, dysplastic and regenerative nodules, intrahepatic bile duct adenoma, and cholangiocarcinoma, whereas peliosis should be differentiated from an associated-cavernous hemangioma. Regarding the preoperative diagnosis, ultrasonography, computed tomography, and MRI examinations are commonly used but differential diagnosis of HA versus HCC is very difficult. Biopsy is necessary for diagnostic confidence and adenomas larger than 4 to 5 cm, in male patients and/or patients with cirrhosis, should be surgically resected. Moreover, no specific features about differentiation of HA from AHN are known. The MRI is usually used to subclassify HAs in steatotic, peliotic, and mixed (steatotic and peliotic) type. However, both steatotic and peliotic adenomas shows, according to Lewin et al., hyperintense signal on T1- and T2-weighted images and moderate enhancement at the arterial phase. The steatotic adenomas are usually smaller than 7 cm in diameter, compared to the peliotic type that can be larger. At contrasting MRI, no delayed enhancement is observed in steatotic type, whereas the peliotic-type adenomas can display persistent enhancement at the portal and delayed phase. In the present study, both cases were peliotic lesions. In first case, due to large peliotic areas, the ultrasonography revealed the suspicion of hemangioma that was removed due to acute hemoperitoneum. The second case showed, at ultrasonography, a nodule larger than 3.5 cm occurring in the setting of cirrhosis; this was the reason why it was surgically removed without any supplementary investigations.

This article showed 2 unusual cases that highlights the difficulties of diagnosis of tumors with peliosis developed in the setting of cirrhosis. The complex differential diagnosis should be based on the clinicopathologic background, histological aspect, reticulin stain, immunoprofile, and cytogenetic analysis of chromosomal abnormalities. The AHN is a histological entity that should be included and codified in the World Health Organization Classification system.

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