Diagnostic particularities in primitive diffuse form hepatocellular carcinoma associated with portal vein thrombosis

I. ROGOVEANU1), DIANA VĂCARU2), D. GHEONEA1), CLAUDIA VALENTINA GEORGESCU3), VIOLETA COMĂNESCU3), T. CIUREA1)

1) Department of Internal Medicine, Division of Gastroenterology, University of Medicine and Pharmacy of Craiova
2) Emergency County Hospital, Craiova
3) Department of Pathology, Emergency County Hospital, Craiova

Abstract
The diagnosis of primitive hepatocellular carcinoma, infiltrative form, arose on liver cirrhosis is often difficult because the imagistic investigations could not relevate the tumoral formation. We are presenting the case of a 56 years patient, diagnosed with viral B liver cirrhosis, in which the clinical symptomatology and laboratory investigations were leading to hepatocellular carcinoma, but the ultrasonography and CT scan could not confirm the malignant transformation. In these conditions we performed ultrasonographically guided biopsy from the liver parenchyma and visualized thrombus in portal vein lumen. Histopathological exam from the thrombus tissue samples confirmed hepatocellular carcinoma diagnosis.

Keywords: liver cirrhosis, hepatocellular carcinoma, portal vein thrombosis, ultrasonographically guided biopsy.

Introduction
Hepatocellular carcinoma (HCC) is an epithelial malignant tumor, which has its origin in hepatic cells (hepatocytes). This disease has an arising incidence (fifth place among the most frequent carcinomas), with predominance in males. In most of the cases, HCC is associated with viral B or C liver cirrhosis and it is diagnosed in advanced stages because it has an asymptomatic initially evolution [1, 2].

Usually, the carcinogenesis is producing through multistage progression of the cirrhosis to hepatocellular carcinoma, intermediated by premalignant lesions like adenomatous hyperplasy and hepatocytes display. Adenomatous hyperplasy term was initially given for atypical nodular lesions developed in a cirrhotic liver, lesions which do not fulfill all the diagnosis morphological criteria for hepatocellular carcinoma but they are considered possible precursors of malignant transformation (borderline nodules) [3, 4].

There were described three types of focal hyperplasic lesions, with:
• glycogen deposing cells (GSF);
• mixt cells (MCF);
• basophiles (FB).

Case report
We are presenting the case of a 56 years old patient, male, admitted in Medical I – Gastroenterology Clinic of Emergency Clinic Hospital Craiova for epigastrial and right upper quadrant pain, important fatigue, and five kilos weight loss during last month.

He had a splenectomy history 11 year ago because of an abdominal traumatism.

Physical examination reveled an overweight patient with muscular hypotrophy at the level of shoulders and hepatocellular failure cutaneo-mucosal signs (jaundice of the sclera, vascular stars in superior vena cava territory, palmar erythema, carmine tongue); no abdominal peritoneal irritation signs; palpation abdominal tenderness in epigastrum and upper right quadrant; liver inferior limit at 3 cm below costal margin, edged, pronounced consistency; signs of ascites.

Results
Clinical aspect was evidently orientated through a severe hepatic disease (cirrhosis or hepatocellular carcinoma), so, biologic, immunologic and imagistic studies were focalized for these entities differentiation.

The laboratory findings were: Hemoglobin = 10 g/dl, Leucocytes = 7.600/mm³, Platelets = 230.000/mm³, AST = 140 IU/l, ALT = 121 IU/l, total Bilirubine = 3.50 mg/dl, absence of HBS antigen and anti VHC antibodies, α-fetoprotein presence.

Abdominal ultrasonography: both liver lobs enlargement, but without visible tissular formations; important dilatation of portal vein (26 mm), with collateral circulation in hepatic hilum and extended thrombosis area up to the level of right and left branches bifurcation; surgical absence of the spleen; normal pancreatic aspect; ascites in small quantity.

CT scan: liver with heterodense structure, with heterogeneous areas in segments IV, V and VI, in portal vein right branch neighboring; without hepatic and pancreatic focal lesions; liquid in peritoneal cavity (Figures 1 and 2).

Upper digestive endoscopy: signs of portal hypertension with presence of grade III varices and
hypertensive portal gastropathy.

Endoscopic ultrasonography: Without pancreatic localized processes, diffuse inhomogeneous left hepatic lobe, without localized formations.

The absence of focal hepatic lesions in a clinical suggestive context for malignant proliferation in viral B liver cirrhosis imposed ultrasonographically guided liver biopsy. We used a semi-automatic needle from Autovac type (1.4 mm) and we have performed two real-time ultrasonographically guided passages.

We collected two samples for histopathological exam – one from left hepatic lobe and the other from portal vein lumen thrombus (Figures 3 and 4).

We decided to perform ultrasonographically guided double-passages liver biopsy from hepatic parenchyma and portal thrombus because, in the presented situation, there is the possibility that portal vein thrombosis to appear in liver cirrhosis context or in hepatocellular carcinoma with vascular invasion.

Tissue collected samples were processed by means of the classical histopathological method of paraffin embedding and were stained with Haematoxylin–Eosin.

Microscopically, a slightly chronic inflammatory infiltrate as well as moderate fibrosis were found at the level of the portal tracts and at the peribiliary level. There were also found many hepatocytes with a swollen, edematous or granulovacuolar cytoplasm and apoptotic hepatocytes with pyknotic nucleus and intensely eosinophilic cytoplasm (Figures 5 and 6).

Isolate hepatocytes with “ground-glass”, fine granular, eosinophilic cytoplasm were also present. Microscopy images confirmed liver cirrhosis diagnosis; they showed thick fibrous bridges that delimit regenerating nodules (containing binucleated hepatocytes with basophilic cytoplasm), but they also showed hepatocellular carcinoma development on liver cirrhosis lesions (Figure 7).

Histological transformations suggestive for hepatocarcinoma were found in hepatic parenchyma adjacent to portal vein and in tissue samples prelevated from portal thrombus. Thus, we observed the presence of the typical aspect of well-differentiated hepatocellular carcinoma with trabecular pattern, supported by a minimal connective tissue and with scarce clear cells containing cytoplasmatic glycogen. Tumor cells had moderate variation in cell and nuclear size and shape but retain their resemblance to normal liver cells (Figure 8).

In these conditions, correlation between clinical tests, laboratory and histology allowed the diagnosis of primitive hepatocellular carcinoma, diffuse form, portal vein malignant thrombosis and uncompensated viral B liver cirrhosis.

Discussions

Portal vein thrombosis, described for the first time in literature by Balfour and Stewart (1968), can appear in many diseases, most frequently in liver cirrhosis, pancreatic and liver carcinomas, chronic myeloproliferative syndromes and, rarely, in congenital or gained coagulation diseases (C and S protein deficiency, antithrombin deficiency, antiphospholipid syndrome) [5–7].

The diagnosis is ultrasonographically established by visualization of a hyperchoic formation, intraluminale situated, which obstruct venous flux and determine collateral circulation development and the blood deviation from portal vein to cave territory (portal cavernoma) [8–10].

MCF is predominant in cirrhotic patients with a high risk of hepatocarcinoma. Large or small cells hepatic display is an intermediate phase on progression from the dysplastic phenomena to the neoplastic one. The different phases of multistage carcinogenesis, including the initially genotoxic aggression (initiation), the development of a premalignant population to a tumor (promotion) and the clonal expansion (progression) are under the influence of some genes which control the apoptosis (programmed cellular death) [11, 12].

Normally, the genotoxic events lead to DNA repairment or to cells destruction through apoptosis (if DNA modifications are too deep).

The presence of p53 gene mutations or Bcl-2 production increasement inhibits the apoptosis, permitting mutant cell surviving [12, 13].

Macroscopically, hepatocellular carcinoma has a variable aspect and it is classified in three types:

- solitary (massive) – unique encapsulated tumor or diffuse delimited; frequently, it appears on previous healthy liver;
- multifocal;
- infiltrative (diffuse) – difficult to differentiate of neighboring liver tissue; usually, it is associated with liver cirrhosis.

Hepatocellular carcinoma extension inside the liver appears through sanguine vessels or directly invasion, most often in portal vein or its branches.

In medical practice, diagnostic difficulties appears, most of the cases, in diffuse infiltrative carcinomas developed on liver cirrhosis because the imagistic examinations, even the state of art ones, cannot precisely establish malignant or benign nature of the lesions [14–16].

As we mentioned above, hepatocellular carcinoma appearance on liver cirrhosis is not at al rarely. The difficulties, which usually the physician is confronted with, appear in infiltrative diffuse forms. In these forms, although clinical findings and some of the laboratory tests suggest malignant transformation, imagistic methods, even state of art ones (endoscopic ultrasonography, computer tomography, etc.) could not certificate this.

In these conditions, ultrasonographically guided liver biopsy is the only available method that permits tissue sample collecting for histological examination and for certitude diagnosis, although it is very difficult to perform it in territories with good vascularisation and high risk of hemorrhage or difficult reachable territories (portal vein thrombosis) [17–19].
Diagnostic particularities in primitive diffuse form of hepatocellular carcinoma associated with portal vein thrombosis

Figure 1 – Abdominal CT: liver with heterodense structure, with heterogeneous areas in segments IV, V and VI, in portal vein right branch neighboring

Figure 2 – Abdominal CT: portal vein right branch thrombosis; without hepatic and pancreatic focal lesions; liquid in peritoneal cavity

Figure 3 – Abdominal ultrasonography: portal vein thrombosis

Figure 4 – Ultrasonographically real-time guided liver biopsy from the thrombus
Figure 5 – Portal and perilobular inflammation and fibrosis (HE staining, ×100)

Figure 6 – Hepatocellular degenerescence aspects in many hepatocytes (HE staining, ×400)

Figure 7 – Regenerating nodules (liver cirrhosis) area (right) and hepatocarcinoma area (left) (HE staining, ×100)

Figure 8 – Thrombosis area detail (HE staining, ×200)
Conclusions

Presented case shows diagnostic difficulties in patients with diffuse forms of hepatocellular carcinoma and portal vein thrombosis, in which the imagistic tests cannot confirm tumoral circumscribed formations.

The particularity of the diagnosis is the histological exam of portal thrombus with typical malignant transformation.

The particularity of the diagnosis is the histological exam of portal thrombus with typical malignant transformation.

References


Mailing address

Ion Rogoveanu, Associate Professor, M.D., Ph. D., Department of Internal Medicine, Division of Gastroenterology, University of Medicine and Pharmacy of Craiova, 1 Tabaci Street, 200642 Craiova, Romania; Phone +40251–412 367, E-mail: mogoanta@umfcv.ro

Received: February 28th, 2006
Accepted: March 30th, 2006