PORTAL VEIN THROMBOSIS AND DUODENAL TUMOUR IN A PATIENT WITH MULTICENTRIC HEPATOCELLULAR CARCINOMA: CASE REPORT

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Abstract: *The hepatocellular carcinoma (HCC) is the most common malignant hepatic tumour and also the main cause of death with an increasing incidence worldwide.(1) Despite the on-going progress of the prevention techniques, the screening and the new technologies of diagnosis and treatment, the incidence and mortality of these conditions continue to grow. Cirrhosis remains the most important risk factor for HCC development, regardless of etiology, while hepatitis B and C are independent risk factors for the occurrence of cirrhosis. Chronic consumption of ethanol remains an important supplementary risk factor, since alcohol abuse is five times more common than hepatitis C.(2) We hereby present the case of a patient with multicenter hepatocellular carcinoma whose condition has rapidly evolved unfavourably despite the antiviral therapy (portal vein thrombosis and duodenal tumour), thus limiting the therapeutic options.*

INTRODUCTION

The hepatocellular carcinoma (HCC) is the most common malignant hepatic tumour and also the main cause of death with an increasing incidence worldwide.(1) GLOBOCAN estimates that in 2012, in Romania, the hepatic cancer is ranked 10th among men and 15th among women.(3,4) A major risk in developing HCC is represented by the infections with hepatic viruses B and C, aflatoxin exposure, hereditary diseases (hemochromatosis, α1 antitrypsin deficiency, Wilson disease, tyrosinemia) and alcoholic liver disease. The latest epidemiological researches have included on the list of risk factors the metabolic syndromes, diabetes mellitus type II, and nonalcoholic liver steatosis.(4,5)

CASE REPORT

The 67 year-old patient had been suffering from chronic viral hepatitis since 2009 and received treatment with peginterferon and ribavirin for six months, with no virological response. During May-June 2016 he underwent treatment with ombitasvir, paritaprevir and ritonavir, in association with dasabuvir. He also had a history of hypertension, gallbladder lithiasis, and anxious depressive disorder. The patient presented with marked physical asthenia, fatigue, loss of appetite and weight loss (approximately 7 kg in two weeks), and diffuse abdominal pain.

The objective examination revealed a relatively good condition, afebrile, overweight (body mass index - BMI of 29.3 kg/m²), pale teguments and membranes, vascular stars and telangiectasia located on the face and on the anterior and posterior thorax, bilateral trophic disorders in the calves, bilateral vesicular murmur, ventricular aura = 70b/min, blood pressure = 120/70 mmHg, painful abdomen in the right upper quadrant, the liver with lower right lobe edge at 8cm below costal margins, and the spleen with the inferior pole at 2 cm under costal margins. The lab tests revealed the following: Hemoglobin (Hb) 5,0 g/dL, Hematocrit (Ht) 17,0 %, average erythrocyte volume 102 fL, thrombocytes count 228 10^3/ul, total bilirubin 0,39 mg/dL, serum creatinine 0,57 mg/dL, serum alkaline phosphatase 99U/L, 100 U/L, Glycaemia 110 mg, γ- glutamyl transferase (GGT) 100/dL, reactive C protein 32,76 mg/L, Aspartate aminotransferase (TGO) 95 U/L, Alanine aminotransferase (TGP) 52 U/L, Urea 32 mg/dL, PT 15,3 s, prothrombin activity 65,6%, Interational Normalized Ratio (INR) 1,27, Sideremia 28,2 µg/dL, total proteins=6,6g/dl, albumin 54.2%, alfa1-globuline 8.2%, beta1-globuline 4.1%. Alfa fetoprotein (AFP) 256 UI/ml.

The abdominal ultrasound has detected: liver with irregular capsular contour, diffuse inconsistent and micronodular echostructure, a formation present at segment V, five hypoechoic nodular formations of 3/6/22/8, respectively 2.7 cm in diameter; the right branch of the portal vein is not visible; the portal vein = 17mm, main biliary tract = 5mm, splenic vein retropancreatic 10mm; relaxed cholecyst with hydropic aspect, with the lumen entirely occupied by ecogenous sediment and several gallstones, (the biggest measures approximately 2 cm and is located in the infundibulo-cystic area); the spleen – long axe of 15,2cm with homogenous structure; small amount of perihepatic fluid. The abdominopelvic CTscan examination native and post contrast iv, with contiguous sections, has revealed: a iodophilic mass in hepatic with subhepatic evolution and local-regional invasion; hepatic nodules hypofixed at the right lobe; thrombosis of the portal vein trunk and its intrahepatic branches in the right lobe; hypertension; homogenous splenomegaly; retroperitoneal adenopathies; right pleural fluid in small amount; ascites in small amount; retracted conglomerate bronchiectasis in posterior segment of upper right lobe.

Figure no. 1. Portal vein thrombosis

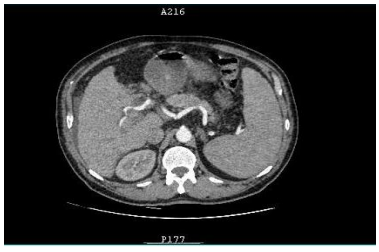

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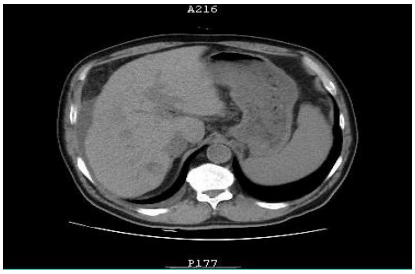
Figure no. 2. Multicentric hepatocarcinoma with duodenal metastasis



The upper digestive endoscopy has shown an ulcerous prepyloric lesion.

Ensuing the clinical and paraclinical investigations, the following diagnoses were established: multifocal hepatocellular carcinoma (clinic diagnosis, echography, CT + biochemical - alfa fetoprotein 256 U/L), severe iron deficiency anemia (Hb 5g/l) due to an ulcerous prepyloric lesion detected at the endoscopy (which is why the liver biopsy puncture was synchronized with the histopathological confirmation of the neoplasia), portal vein thrombosis, gallbladder vesicular lithiasis. During hospitalization, the patient underwent treatment with antihypertensive, hepatoprotective and antiemetic medication, as well as 2 units of erythrocyte concentrate (CER), with a slightly favourable evolution. When discharged, the patient was recommended to be taken into evidence by the Oncologic Department, in order to establish the chemotherapeutic treatment.

On February 27th, 2017, the patient came to the Oncology presenting melena, asthenia, and fatigue. The objective examination showed a fairly good clinical condition, IP=3, pale teguments and mucosa, palm erythrosis, and hepatosplenomegaly. The patient had a loss of appetite; he was afebrile, with voluminous abdomen due to ascites fluid, with no pains and with melena.

The laboratory analyses have shown the following: Hb 6.8 g/dl, GGT 123 U/L, TGO 78 U/L, TGP 70 U/L, Serum iron 12.8 ug/dL, Ferritin 40.2 ng/ml. The upper digestive endoscopy was repeated, thus revealing the tumour occupying the lumen at the level of the duodena. Biopsies were performed and the histopathological exam exposed a fibrin leukocyte exudate, with mixed inflammatory infiltrate and two glandular elements with retained mucus secretion, with reactive nuclear modifications (irregular and slightly enlarged nuclei with hyperchromia).

Following the interdisciplinary consultation (surgeon, oncologist and gastroenterologist) the case was considered to be outside the therapeutic surgical and oncological resources, given the cirrhotic pathology and the local and regional extension of the disease; the treatment was symptomatic and it consisted of iron based medication and 4 U CER isogroup, isoRh, gastric antisecretory drugs, hemostatic medication, well-tolerated by the patient. He was discharged with a slightly improved general condition and a recommendation for hospitalization in a specialized palliative care center.

DISCUSSIONS

A major risk factor in the development of HCC is represented by the chronic infection with hepatitis C virus. HCC occurs only after two or more decades after infection, and the major risk of malignity occurs in patients with advanced fibrosis and hepatic cirrhosis. The main factors that influence the occurrence of HCC among individuals infected with hepatitis C virus include: male gender, advanced age, co-infection with B virus, ethanol consumption, and type II diabetes mellitus.(6)
Hepatitits C Virus (HCV) infection cause chronic inflammation, cellular death, proliferation and hepatic cirrhosis.(7) Thus, HCC associated with HCV occurs in most cases in patients with hepatic cirrhosis.(7) The risk of HCC occurrence is high in patients infected with HCV (8), although the percentage varies according to the degree of hepatic fibrosis at the time of HCV infection.

HCV belongs to the Hepacivirus genus of the Flaviviridae family.(9) HCV is an ARN virus unable to integrate in the genome of the host cell. Through indirect mechanisms, HCV determines the occurrence of HCC. The core protein of HCV enters the host cell and locates on the outside of the mitochondrial membrane, as well as in the endoplasmic reticule, and triggers oxidative stress. This results in the activation of the key signalizing pathways such as the p38 mitogen activated protein kinase and that of kappa B nuclear factor, leading to increased regulation of genes involved in cytokine production and subsequent inflammation that induce the modification of apoptotic pathways and tumor formation.(10) The nonstructural proteins of HCV, NS3 and NS5A are also considered key mediators as they induces oxidative stress and inflammation.(10)

It has been demonstrated that HCV infection induces insulin resistance (IR), which in turn is highly connected to the development of fibrosis and the occurrence of type II diabetes mellitus.(11)

An additional factor in patients with hepatic cirrhosis caused by hepatic C virus is represented by ethanol consumption. These particular patients develop a more severe form of hepatic cirrhosis and have higher incidence of cirrhosis and HCC as compared to patients with hepatic insufficiency.(12) Also, it has been shown that the risk of developing HCC increases as the quantity of consumed ethanol increases.(13) The mechanisms by which alcohol aggravates HCV related liver disease are yet to be clarified; one of the variants would be the increased replication of HCV in the presence of alcohol; alcohol related changes in the hypervariable region of the viral genome lead to HCV liver disease aggressiveness and resistance to therapy with interferon.(6,12) Nevertheless, the dominant mechanism for the synergism between alcohol and HCV infection seems to be the increase of the oxidative stress. As we mentioned above, the HCV core protein stabilizes the mitochondrial membrane and sustains the oxidative stress. The ethanol potentiates the mitochondrial damage by increasing the production of oxygen reactive species and by amplifying the hepatic oxidation of glutathione. Moreover, alcohol and HCV core protein act synergistically, by causing lipid peroxidation and the increased hepatic expression of TGF-β and TNF- α.(12)

Coffee and vegetable consumption may have a protective role against HCC occurrence. One of the hypothesis that sustain the protective role of coffee refers to the fact that it decreases the serum levels of γ-glutamyl transferase (GGT) which in turn are associated to a smaller incidence of HCC occurrence.(14) HCC on non-cirrhotic liver is less common and it is mainly caused by hepatitis B virus infection.(15) However, the non-cirrhotic liver may be affected by HCC as a result of contamination of food products with aflatoxin B1 (type of mycotoxin produced by Aspergillus which can easily grow on food products when stored in inappropriate conditions). When ingested, it is metabolized into AFB1-exo-8,9-epoxide, which binds to hepatocyte DNA, and causes lesions. AFB1 is also responsible for producing mutations in the p53 tumour suppressor gene.(16,17)

The screening for hepatocellular carcinoma is recommended for all the patients with hepatic cirrhosis or with chronic viral hepatitis with B and/or C virus; this less expensive method is very useful in early detection of the disease. The

ultrasound is recommended especially for individuals with risk at an interval of 3-4 months as well as the AFP dosing every 6 months.(18)

The tumour thrombosis of portal vein (PVT) is the most common form of macrovascular invasion of HCC. Almost half of the HCC patients have portal vein thrombosis at the moment of diagnosis. The patients with PVT are more susceptible to metastases at the moment of diagnosis, the therapeutic options are more reduced, while the global survival rate is lower as compared to patients without PVT.(19) The poor prognosis of PVT in patients with HCC comes as a result of several factors: impaired hepatic reserves, intrinsic tumour aggressiveness, low tolerance to chemotherapy and complications due to portal hypertension.(20)

REFERENCES

1. El-Serag HB, Hepatocellular carcinoma and hepatitis C in the United States. 2002 Nov;36(5 Suppl 1):S74-83, Accessed in 18.03.2018.
2. Fateen W, Ryder SD, Screening for hepatocellular carcinoma: patient selection and perspectives. 2017 May 17;4:71-79. doi: 10.2147/JHC.S105777, eCollection 2017, Accessed in 02.04.2018.
3. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012, Cancer Incidence and Mortality Worldwide, IARC Cancer Base No.11(Internet). Lyon, France: International Agency for Research on Cancer; 2013. http://globocan.iarc.fr, Accessed in 28.03.2018.
4. Grigorescu M, Irimie A, Beuran M, Tratat de oncologie digestivă, Editura Academiei Române, Bucureşti. 2014;II:43-59.
5. Tornillo L, Carafa V, Richter J, et al. Marked genetic similarities between hepatitis B virus –positive and hepatitis C virus –positive hepatocellular carcinomas, J Pathol. 2000;192:307-312. Accessed in 29.03.2018.
6. Sanyal AJ, Yoon SK, Lencioni R. The etiology of hepatocellular carcinoma and consequences for treatment, Oncologist. 2010;15 Suppl 4:14-22. doi: 10.1634/theoncologist.2010-S4-14, Accessed in 27.04.2018.
7. But DYK, Lai CL, Yuen MF, Natural history of hepatitis-related hepatocellular carcinoma, World J Gastroenterol. 2008;14:1652-1656. Accessed in 23.03.2018.
8. Donato F, Tagger A, Gelatti U et al. Alcohol and hepatocellular carcinoma: The effect of lifetime intake and hepatitis virus infections in men and women. Am J Epidemiol. 2002;155:323-331.
9. Szabó E, Páska C, Kaposi Novák P, et al. Similarities and differences in hepatitis B and C virus induced hepatocarcinogenesis, Pathol Oncol Res. 2004;10:5-11.
10. Sheikh MY, Choi J, Qadri I et al. Hepatitis C virus infection: Molecular pathways to metabolic syndrome, Hepatology. 2008;47:2127-2133.
11. Lonardo A, Adinolfi LE, Petta S et al, Hepatitis C and diabetes: The inevitable coincidence?, Expert Rev Anti Infect Ther. 2009;7:293-308.
12. Singal AK, Anand BS, Mechanisms of synergy between alcohol and hepatitis C virus, J Clin Gastroenterol. 2007;41:761-772.
13. Donato F, Tagger A, Gelatti U, et al. Alcohol and hepatocellular carcinoma: The effect of lifetime intake and hepatitis virus infections in men and women, Am J Epidemiol. 2002;155:323-331.
14. Gallus S, Bertuzzi M, Tavani A, et al. Does coffee protect against hepatocellular carcinoma? Br J Cancer. 2002;87(9):956-959.
15. Abdel-Wahab M, Mostafa M, Sabry M et al. Aflatoxins as a risk factor for hepatocellular carcinoma in Egypt, Mansoura Gastroenterology Center study, Hepatogastroenterology. 2008;55(86-87):1754-1759.
16. Bressac B, Kew M, Wands J et al, Selective G to T mutations of p53 gene in hepatocellular carcinoma from southern Africa, Nature, 1991; 350(6317): 429–431.
17. Nuţu V, Epidemiologia, etiopatogenia şi diagnosticul hepatocarcinomului, Jurnalul de Chirurgie, Iaşi. 2011;7(1).ISSN 1584 – 9341], http://www.jurnaluldechirurgie.ro/jurnal/docs/jurnal111/art%2002_vol%207_2011_nr%201.pdf, Accessed in 02.12.2017.
18. Jakab Z. Diagnostic imaging for the screening of hepatocellular carcinoma, Orv Hetil. 2010; 151(27): 1083-10
19. Quirk M, Kim YH, Saab S, Lee EW. Management of hepatocellular carcinoma with portal vein thrombosis, World J Gastroenterol. 2015 Mar 28; 21(12): 3462-3471, Published online 2015 Mar 28. doi: 10.3748/wjg.v21.i12.3462.
20. Chan SL, Chong CCN, Chan AWH et al. Management of hepatocellular carcinoma with portal vein tumor thrombosis: Review and update at 2016. World Journal of Gastroenterology. 2016;22(32):7289-7300. doi:10.3748/wjg.v22.i32.7289