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Primary hepatocellular carcinoma in HBV infected patient - a case report

Patrycja Łanowy[1], Krystian Ślusarz[1], Paulina Kurdyś[1], Miłosz Bichalski[1], Barbara Sobala-Szczygieł[1], Jerzy Jaroszewicz[1]

[1]Department of Infectious Diseases and Hepatology, Medical university of Silesia in Katowice, Poland
E-mail adresses: patrycjalanowy@gmail.com[1]

ABSTRACT:

Hepatocellular carcinoma is primary neoplasm of the liver, which usually accompanies cirrhosis of this organ. This malignancy neoplasms commonly occurs all around the world. The frequency of morbidity on this disease is correlated with frequency of HBV and HCV infections in the population. That is caused due to the pathogenic effects of these viruses, among others on liver cells, affecting carcinogenesis. Appropriate and early treatment of infection reduces the chance of developing cancer. In our article we present the case, 63-years-old male, with primary hepatocellular carcinoma correlated with hepatitis B virus infection. Unfortunately, the neoplasm was diagnosed too late, and despite the comprehensive treatment introduced, the patient died.

KEY WORDS: primary hepatocellular carcinoma, HCC, HBV infection

INTRODUCTION

Hepatocellular carcinoma (HCC), according to the newest literature, is second cancer in the world, with the highest mortality (1). In 2012 almost 782,500 HCC cases were diagnosed worldwide, this year number of deaths caused by this neoplasm reaching 745,500 (2). Mortality is higher among men, with a peak incidence at age 70 (3,4). The most cases occurs in East and Southeast Asia as well as in Sub-Saharan Africa. There has been an increase in morbidity in Western Europe and the United States in recent decades (5).

The etiological of HCC factors include liver cirrhosis associated with alcohol abuse, non-alcoholic fatty liver, cirrhosis associated with a viral infection, male sex, smoking, obesity, type 2 diabetes, advanced age. Infection with HBV, HCV, and alcohol abuse are the greatest risk factors (2,5,6). 54.4% of world total HCC is associated with HBV, while only 20% with HCV (7).

Diagnosis of genetic types among patients with a higher risk of developing HCC would allow for rapid intervention and improvement of treatment results. For this tumor, high frequency of MAGE gene expression is described. Specific markers for the dissemination of this type of tumor is the expression of the MAGEA1 and MAGEA3 genes. In the case of CASG Genes, CSAG1 was overexpressed in the case of HCC cell proliferation (6).

The development of HCC is the most dangerous complication of HBV infection, and despite the existence of an effective vaccine, 257 million people suffered from chronic infection in 2015. Estimated data state that 8-20% of patients with chronic hepatitis B (CHB) - who are not treated - will develop cirrhosis within 5 years, while 2-8% of them develop HCC annually (5). Co-infection with HBV and HCV does not cause an increased risk of developing HCC compared to separate infections (8).

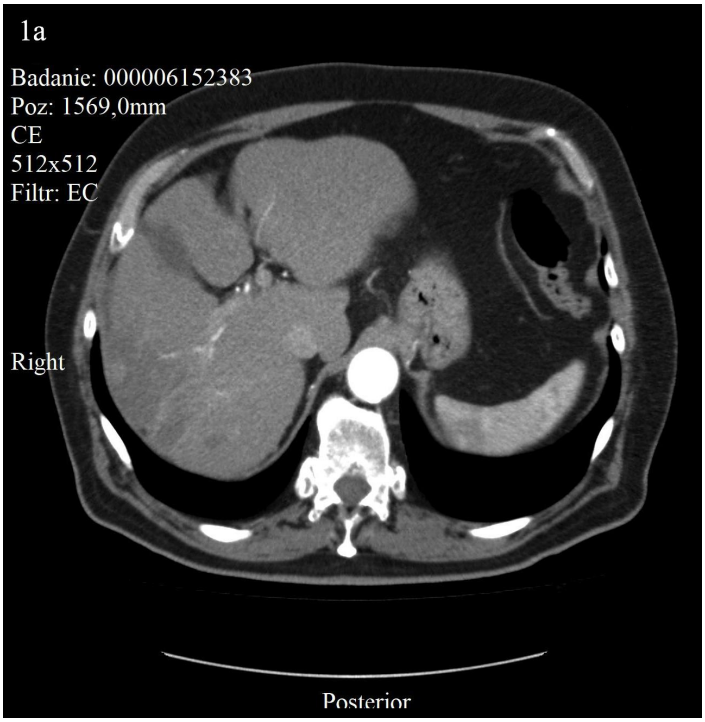
To a screening test for HCC include ultrasounds and measurement of alpha-fetoprotein (AFP) level in blood, unfortunately, the sensitivity of the last test turns out to be insufficient (4,5). However, increased AFP level remain a factor that increases the likelihood of developing HCC compared to people who have low levels of this marker (9).

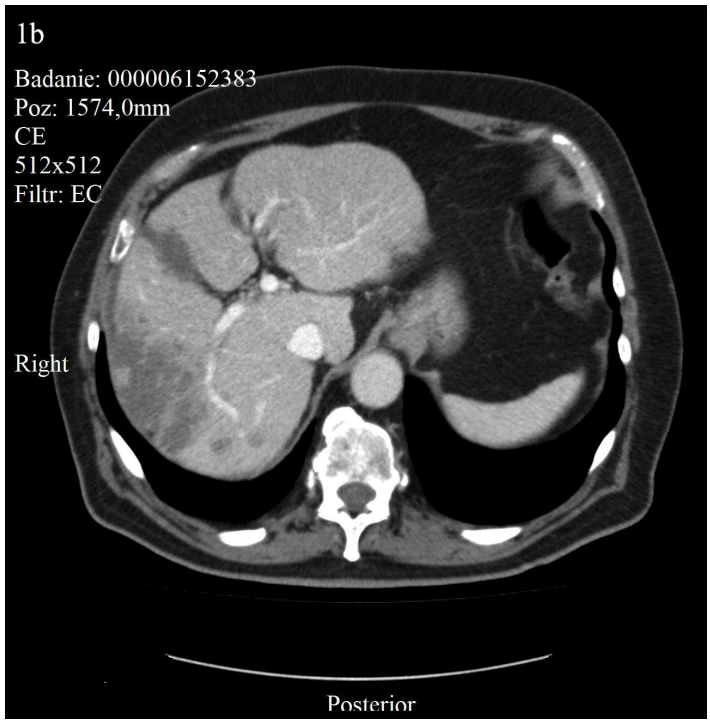
Therapeutic management has changed over the last decades. In

the past, treatment was performed by surgical resection, but new methods were needed in case of multiple tumors and metastases (10). Surgical resection is achievable among patients with single HCC with normal liver function and no portal hypertension. However, the most effective method is resection along with liver transplantation, wherein addition to correct treatment the survival rate over 5 years is 60-80% (4). Besides, most patients do not qualify for surgery because of the high stage of the disease at the time of diagnosis (1). In patients with HCC in BCLC-B stage (asymptomatic, multifocal, without metastases outside the liver and without infiltration) chemoembolization treatment is recommended (TACE). Among patient with HCC in BCLC-C stage with adequate liver function, sorafenib is the first-line treatment (4).

CASE REPORT

A 63-years-old male patient, he was admitted to the hospital, in 2013, an emergency condition - esophageal variceal hemorrhage. The patient had not been previously treated or diagnosed due to liver disease. While searching for the causes of the incident, an examination of the liver with ultrasounds was performed and revealed a focal change inside the organ. The medical history of the patient of the revealed that the patient myocardial infarction in the past, also patient were currently under treatment due to hypertension. The patient was referred to a hepatology clinic where computed tomography (CT) of the abdomen was ordered. The CT scans showed two focal lesions in VII segment of the liver - the diameter was 50 and 35 mm (Figure 1). Blood tests were also ordered and revealed a high level of AFP (alpha-fetoprotein) (11). This protein is a marker of the malignancy neoplasms, its increased level may be a sign of liver neoplasms, but also hepatitis and cirrhosis (4). Alanine aminotransferase (ALT) and aspartate transaminase (AST) levels were slightly increased, also gamma-glutamyl transpeptidase level exceeded the norm more than 40 times. The patient was tested for the presence of Hbs Ag protein - the result was positive - the patient was a carrier of HBV.





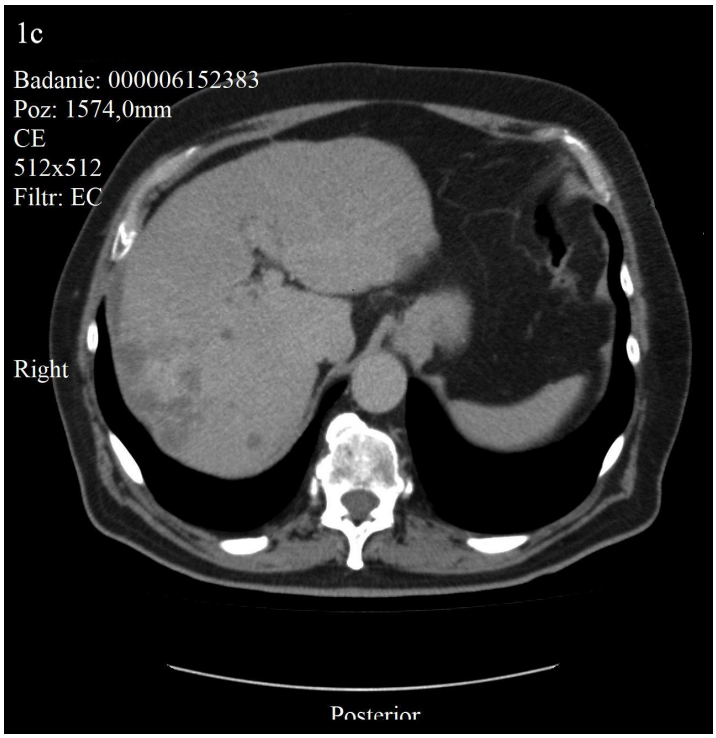


Figure 1a, 1b, 1c. The typical hallmark is the combination of hypervascularity in late arterial phase (defined as arterial phase hyperenhancement [APHE]) and wash-out on portal venous and/or delayed phases, which reflects the vascular derangement occurring during hepatocarcinogenesis.

Table 1. Result of blood tests of the patient.

Tested parameters	**Level**
HBs Ag	+
HBc Ab total	+
HBV DNA	-
HCV Ab	-

Three weeks after CT, the patient underwent liver oligobiopsy. The histopathological procedures revealed that organ's architecture was disturbed - arising regenerative nodules were visible. Limiting lamina was interrupted by an inflammatory infiltration on 50% of its circumference. The periportal spaces were widened by inflammatory lymphoid infiltration of medium degree. To the liver's parenchyma adhered hepatocellular carcinoma (HCC) with trabecular growth pattern, also with necrosis and features of fibrous desmoplasia. The image of the pathological lesions in the histopathological examination indicates on hepatocellular carcinoma in stage G2. (Figure 2,3)

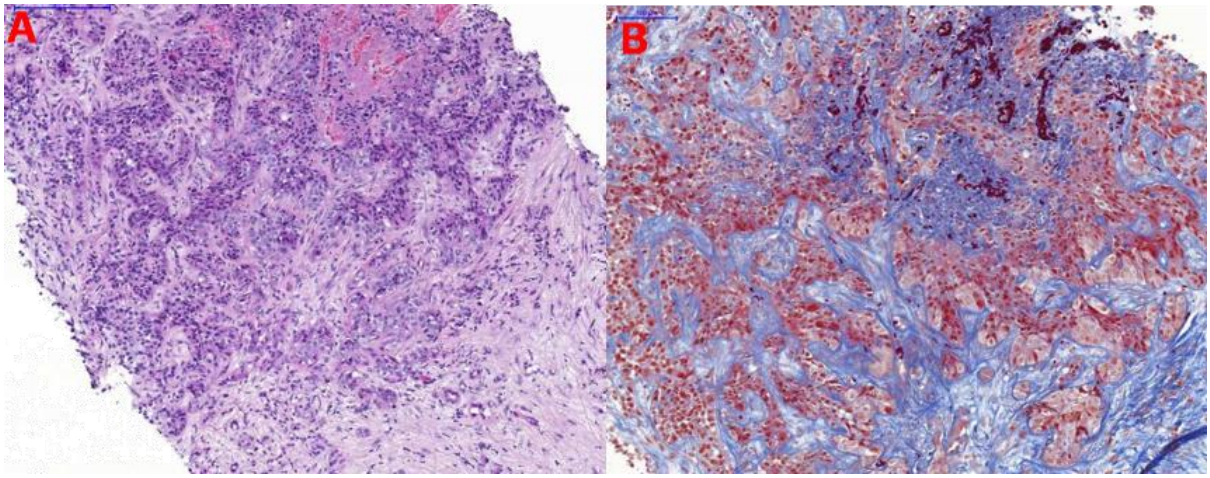


Figure 2. Picture A - liver biopsy at 200x magnification -the fibrous dysplasia is visible. The histological preparation from photo B was stained with the Azan three-color method.

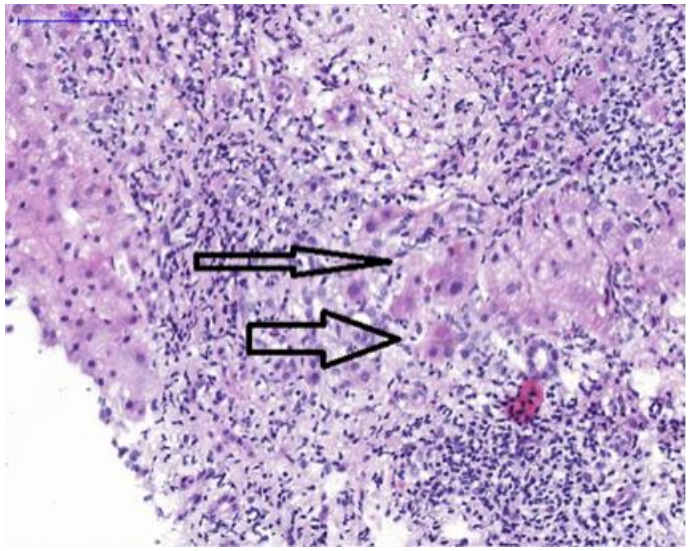


Figure 3. Liver biopsy at 400x magnification, cirrhosis is observed. The arrows point to Mallory body.

Patient unfortunately, was disqualified to orthotopic liver transplantation (OLT), due to the size of the tumor. Chemoembolization of the hepatic artery with Doxorubicin and Lipidol was performed. In October of the same year, an HBV DNA test was performed with a result of 35 U/L, that indicates the HBV infection. Due to this fact lamivudine at a dose of 100 mg/d was included. Subsequent CT examination revealed a poorly demarcated 55x45 mm lesion in segment VII of the liver. The pathological change was hyperdense in the center and it undergoes a slight contrast enhancement in the arterial phase (Figure 4).

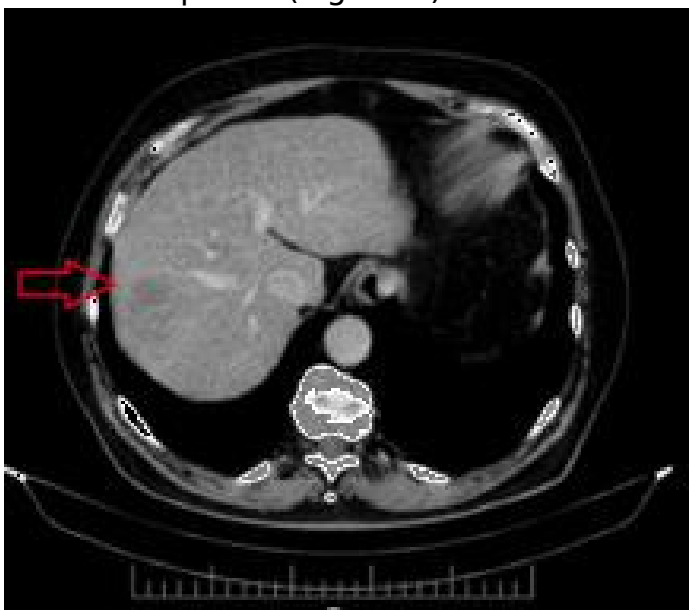


Figure 4. The hyperdensic pathological lesion in VII segment of the liver, revealed on CT scan.

The patient started treatment with Sorafnib, and recived 6 cycles in next 5 months. The results of the patient's blood tests were as follows:
-AST 51U/l ALT 32U/l, albumins and proteins in norm - what suggest that liver perform its function,
-HBV DNA 2976U/l - the earlier level of HBV DNA was undetectable- the increase of its level suggest reactivation of virus' replication.

The treatment with Entecavir 1,0 was implemented and in the March of 2014, the HBV DNA level in the blood was negative.

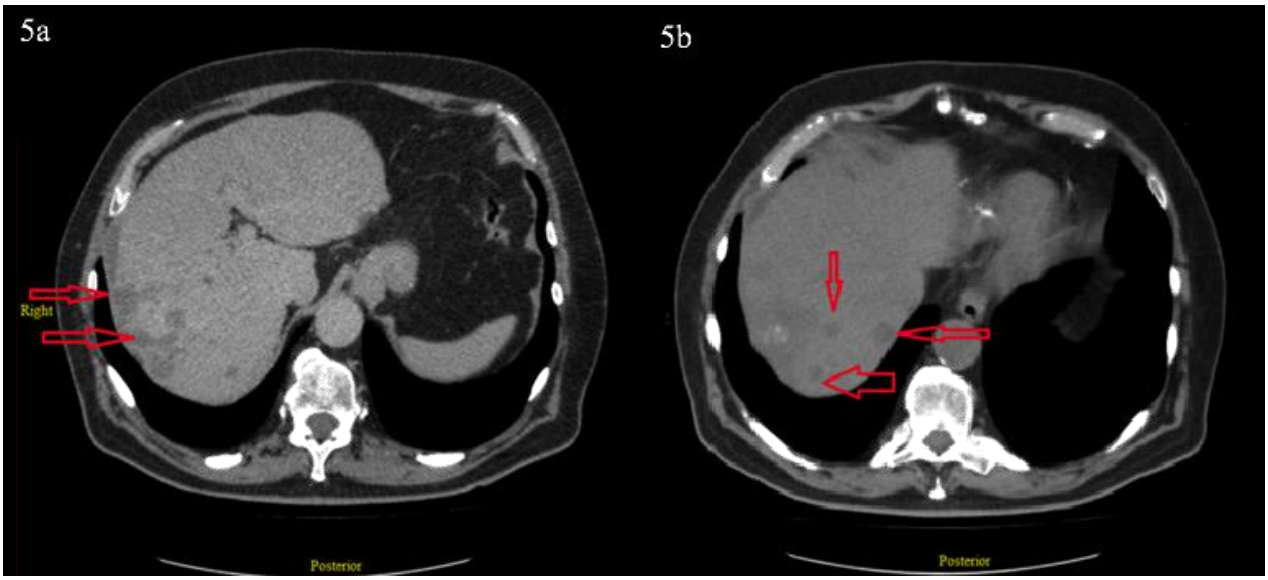


Figure 5a, 5b. The computed tomography of the patient performed in March of 2014.

Another tomography was performed in March 2014 and showed the expansion of cancerous lesions. The patient was qualified for second-line treatment. Three cycles of chemotherapy were given - doxorubicin monotherapy. The patient tolerated the treatment well. Chemotherapy was completed on July 25, 2014. Unfortunately, in August of 2014 the patient died as a result of a disseminated tumor process.

DISCUSSION

The morbidity on HCC has been increasing during recent years (5). In 2016, only 10.5% of HBV infected, which is one of the main factors of HCC, were aware of their infection, and only 4.5 million diagnosed were under proper antiviral therapy (12). Based on this, it can be suggested that there is little public awareness of the risk of the consequences of hepatitis B virus infection. The described patient was at high risk of developing hepatocellular carcinoma due to his gender - the disease

affects men more often; age (63 years) - the peak morbidity of HCC falls in the age of 70, and infection with oncogenic HBV that can lead to the development of this cancer (2,5,6).

The treatment was initially based on the use of chemoembolization (TACE) (two cycles) - that the treatment was carried out following the guidelines presented in the classification of The Barcelona Clinic Liver Cancer (BCLC) for HCC grade B - the average survival time in this type of therapy is 20 months.

After control CT, dafter previously applied therapy, BCLC-C compliant treatment with sorafenib was applied -the average survival time, while using this type of therapy, is 11 months (13). From the moment of histopathological examination of biopsy and making a diagnosis, the patient survived around 12 months. The alarming lesion in the liver was noticed 6 months before the biopsy was made.

CONCLUSION

An important indicator of success in the treatment of cancer is the speed of its detection, qualification, and implementation of appropriate treatment. The correlation of HBV with primary hepatocellular cancer is widely described and proven - hence early detection and treatment of infection with this virus is also important. Currently, HCC is often detected with delay, when surgical treatment and liver transplantation are no longer possible. Targeted researches are needed to improve the detection and treatment of HBV infection and HCC. It is worth noting here that even in people, infected with this virus, with undetectable HBV DNA there is a risk of cancer transformation and these people must be systematically examined. Reactivation of HBV replication should be expected in patients with HBsAg absent in the event of HCC.

The necessary is the invention of cheap, easy-to-use and non-invasive biomarkers for HCC that could be used in high-risk patients to identify those at an early stage of the disease - when many effective treatment methods are possible to use. Improvement of the imaging methods that could distinguish between early HCC lesions and regenerative nodules would complement biomarker screening.

Once HCC occurs, antiviral therapy is likely still beneficial. The goals of therapy in this instance include HBV DNA inhibition, preservation of liver function, prevention of further disease progression, reduction in the risk of flares, reduction in the risk of HCC recurrence, and hopefully improvement in survival.

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