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HEPATOCELULAR CARCINOMA PRESENTING WITH PYREXIA AND LEUKOCYTOSIS: A CASE REPORT

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Summary

Introduction. This type of hepatocellular carcinoma is characterized by fever and persistent leukocytosis. Case report. This is a report of a patient with a long term fever accompanied by persistent leukocytosis. Abdominal ultrasonography revealed a focal lesion in the left hepatic lobe, whereas, computed tomography/magnetic resonance imaging findings were consistent with a liver abscess. The patient received therapy for liver abscess, without improvement. He underwent left lobe segmentectomy 3, with histological features of hepatocellular carcinoma (pseudoglandular type). Conclusion. In patients with focal hepatic lesions accompanied with raised temperature and persistent leukocytosis, without adequate therapeutic response, this clinicopathological type of hepatocellular carcinoma should be considered.

Key words: Carcinoma, Hepatocellular; Leukocytosis; Fever; Liver Abscess; Treatment Outcome; Diagnosis, Differential; Tomography, X-Ray Computed; Magnetic Resonance Imaging; Signs and Symptoms

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver carcinoma, according to most authors accounting for about 80% of all liver cancers; it is the fifth most common cause of death in the male, and the seventh most common cause of death in the female population, while the 5 year survival rate is about 15%. It is associated with a number of risk factors, while its prevalence is different in various regions of the world. HCC mostly develops in the condition of chronic inflammation that has led to liver cirrhosis, so the etiologic factors of chronic liver disease overlap with the factors which account for the development of HCC, like hepatitis C and B virus, alcohol consumption, autoimmune hepatitis, aflatoxin, and recently non-alcoholic liver steatosis [1–3].

Hepatocellular carcinoma is often diagnosed after the appearance of clinical signs and symptoms, mostly thanks to screening programmes for cirrhotic patients and patients with chronic viral hepatitis, sometimes after repeated ultrasound check ups and evaluation of alpha-fetoprotein (AFP) levels, although it has proven to be an incompletely sensitive and specific marker for a successful follow up and diagnosis. Accurate diagnosis of HCC is made by imaging techniques, specific computed tomography/magnetic resonance imaging (CT/MR) findings (so called noninvasive criteria), or by histological analysis of biopsy tissue samples [4–7].

The clinical presentation of HCC is commonly associated with the underlying liver disease, and sometimes it is very hard to differentiate the symptoms of HCC from those of chronic liver disease.

It is well known that HCC is associated with the following symptoms: hepatomegaly, vascular bruising, abdominal pain, portal vein thrombosis, gastrointestinal bleeding, jaundice, eaval invasion, palpable
mass, ascites, ankle edema, etc. Also, laboratory liver tests are in accordance with paraneoplastic syndrome (hypoglicemia, hypocalcemia, erythrocytosis, thrombocytosis etc.), which may be accompanied by skin and neurologic manifestations. HCC may be associated with asthenia, anorexia, weight loss, nausea and fever, all of which may be primary non-specific symptoms [8].

Fever of unknown origin may be the first symptom. It is usually intermittent and accompanied by leukocytosis [9, 10]. Imaging studies play a crucial role in order to rule out liver abscess, or HCC. Hepatocellular carcinoma has different signs and symptoms, depending on the size of the tumor, invasion of vascular structures, presence of cirrhosis and presence of metastases.

Case report

A 69-year-old male patient presented with a two-month history of a burning in the upper part of the abdomen, sweating and raised body temperature (37.5 to 38°C) which usually occurred in the late afternoon. On examination, the patient seemed in relatively good condition, without fever (36.3°C), in a state of cardiopulmonary compensation, without abdominal pain or palpable mass. Laboratory tests revealed leukocytosis of 18.4 (diff white blood cells: neutrophils 74.9%, lymphocytes 14.8%, monocytes 6.9%) and C-reactive protein (CRP) level of 48.7 (reference value below 5). Abdominal ultrasonography was performed (Aplio SSA-770A; Toshiba Medical, Tokyo, Japan), showing an enlarged, fatty liver, with a focal oval lesion in the left hepatic lobe, 38 mm in diameter, not clearly visible, due to the patient’s obesity and aerocolia; the lesion was strongly suggestive of 2 structures, one of which was hyperechoic, the other hypoechoic (Figure 1).

Although he performed a few examinations due to fever of unknown origin, the laboratory results only showed a persistent leukocytosis of 14,59 – 21,70 (with a neutrophilia of 85.2%) despite antibiotic therapy. At that time all the other examined parameters were within reference values.

Since the focal lesion in the left hepatic lobe was of non-specific etiology, a Multidetector CT (MDCT) was performed (MX8000; Phillip Healthcare, Best, Netherlands) revealing an oval heterogeneous hypodense lesion in the left liver lobe with contrast enhancement strongly suggestive of 2 structures, one of which was hyperechoic, the other hypoechoic (Figure 1). The previous medical history showed a chronic heart condition. As part of his routine check-ups, he had an abdominal CT scan a year prior to febrility, without pathological findings.

The differential reading suggested the lesion could be a liver abscess, but MRI was indicated.

The patient received the following therapy: Longaceph 2g parenterally + Metronidazole 3 x 400 mg per os. In the meantime, MRI was performed (1.5 T Avanto; Siemens Healthcare, Erlangen, Germany), showing a well demarcated cystic formation, 14 mm in diameter, remained hypodense, without washout signs in portal venous and venous phases (Figure 2). The differential reading suggested the lesion could be a liver abscess, but MRI was indicated.

Since the focal lesion in the left hepatic lobe was of non-specific etiology, a Multidetector CT (MDCT) was performed (MX8000; Phillip Healthcare, Best, Netherlands) revealing an oval heterogeneous hypodense lesion in the left hepatic lobe, 35 x 25 mm in size. On post-contrast studies, the lesion mostly showed enhancement in the arterial phase while one smaller part of the lesion, 14 mm in diameter, remained hypodense, without washout signs in portal venous and venous phases (Figure 2). The differential reading suggested the lesion could be a liver abscess, but MRI was indicated.

The patient received the following therapy: Longaceph 2g parenterally + Metronidazole 3 x 400 mg per os. In the meantime, MRI was performed (1.5 T Avanto; Siemens Healthcare, Erlangen, Germany), showing a well demarcated cystic formation, 14 mm in diameter, surrounded by a zone of inhomogeneous liver tissue with a maximum diameter of 35 mm. The cystic lesion was only slightly

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**Abbreviations**

HCC – hepatocellular carcinoma

CRP – C-reactive protein

CT – computed tomography

MRI – magnetic resonance imaging

HbsAg – hepatitis C surface antigen

FP – feto protein

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**Figure 1.** Ultrasonography: A focal oval hypo/hyperechoic lesion in the left hepatic lobe

**Slika 1.** Ultrasonografija. Fokalna ovalna hipo/hiperechoena promena u levom režnju jetre

**Figure 2.** Computed tomography: Axial arterial phase tomogram. An oval heterogeneous hypodense lesion in the left liver lobe with contrast enhancement

**Slika 2.** Kompjuterizovana tomografija. Aksijalni tomo-gram u arterijskoj fazi. Ovalna heterogenog hipodenzna promena u levom režnju jetre sa postkontarstnim pojačanjem
visible on T1 weighted tomograms with a high DWI signal, while the zone of the surrounding inhomogeneous tissue was predominantly T2W hyper-/T1W slightly hypointense. After the administration of a paramagnetic contrast, there was a linear increase in signal intensity of the cystic wall, as well as an increase in signal intensity of the peripheral zone to isointensity with liver parenchyma. On delayed post-contrast sequences there was no evidence of a washout effect. In conclusion, the lesion was primarily characterized as a liver abscess, without a certain possibility to exclude other etiology (Figure 3).

After the results of the MRI were read, an abdominal surgeon was consulted, and the patient was referred to the Clinic of Infectious Diseases, where the patient was hospitalized and treated for a liver abscess. During the hospitalization, the patient received Azaran 2 x 2g parenterally and Metronidazole 3 x 500 mg per os for 8 days, followed by 8 days of Tazobactam 4.5 g x 4. A control CT scan was performed 3 weeks later (Somatom sensation 64; Siemens Healthcare, Erlangen, Germany) and showed a persisting inhomogeneous lesion in the left liver lobe (S3), 33 x 28 mm in diameter, with a hypodense zone of liquid density, along with peripheral enhancement in arterial, portal venous and venous phases (Figure 4). The lesion was characterized as an abscess. Since there was no significant change in morphology or size of the lesion, the patient was discharged and referred to a gastroenterologist.

A control ultrasound was performed 10 days later (Aplio SSA-770A; Toshiba Medical, Tokyo, Japan), still showing a focal lesion in the left liver lobe, about 4 cm in diameter, with irregular and spiky margins, oval in shape, with a thin hyperechogenic capsule, with an inhomogeneous structure and a few smaller lesions of different echogenicity (characterized as a nodule within a nodule) (Figure 5). Then, with a persistent leukocytosis, the laboratory results showed: sedimentation rate (SE) 58/108, CRP 59.16, without signs of anemia, alpha fetoprotein (FP) level within reference values, hepatitis B surface antigen (HbsAg) and anti hepatitis C virus (HCV) negative.

The patient was once more examined by an abdominal surgeon, who suggested surgical treatment. The operation was performed about 4 months after...
the fever started, and 2 months after the lesion was seen on the first ultrasound examination (laparotomy, med. superior. segmentectomy lobi hepatis sin. III). The patient’s postoperative recovery was uneventful and gradually he started feeling better. The histopathological report showed that it was a case of hepatocellular carcinoma of pseudoglandular type, HG2, pT1NxMx (immunohistochemical profile: Hepar 1 positive), with evidence of smaller fields of necrosis in the tumor tissue and no pathohistologic characteristics of an abscess. The surrounding liver parenchyma was with signs of micro and macroglandular cirrhosis. The patient was referred to the Oncologic Committee of the Institute of Oncology where a control regimen was planned. A control CT scan of the abdomen was performed 5 months after surgery, and it showed no areas of detectable pathologic density, and the patient was afebrile.

Discussion

There are sporadic cases of HCC described in literature, with clinical manifestations including mainly intermittent fever and leukocytosis [8–10]. Even before the era of CT and MRI, there were rare cases of inflammatory pseudotumors or abscesses associated with increased body temperature and leukocytosis, confirmed to be rare types of HCC mimicking liver abscesses after pathohistological analysis of tissue samples obtained from operated or deceased patients. Among the five published cases, two were patients with cirrhosis, all patients were male (aged 43–79), all with negative (HBsAg), Alpha FP within reference values, except in one case just before death [9]. All patients had intermittent high body temperature (from 36.5 to 39°C), associated with leukocytosis of 15,000 to 100,000 or more, without any response to antibiotics, which was also the case in our patient. Massive necrosis was present in all 5 cases, while our patient presented only with small fields of necrosis in the tissue of pseudoglandular HCC, without pathomorphologic signs of abscess. In most cases of histologically confirmed HCC, it was a poorly differentiated tumor. There are theories that these are tumors with sarcomatoid degeneration [10]. Even though the main parts of the tumor were proven to contain sarcomatoid malignant cells, with fields of trabecular cells and areas of necrosis, it was a case of a poorly differentiated HCC, more so than a combination of sarcoma and HCC [9].

All these tumors were hypovascular on angiography and a possible explanation for this is that the tumor cells were not producing the angiogenic factors, so the lack of neovascularization was the cause of tumor cell necrosis [9]. It is known that tumor-induced granulocytosis can be explained by the production of granulocyte growth factors by tumor cells, while high body temperature is explained by the production of pyrogenic factors of malignant cells or macrophages in response to tumor necrosis.

Due to the aforementioned facts, patients with this type of tumor present with different clinical signs and symptoms compared to those with other forms of HCC. Raised body temperature occurs in 12% of patients suffering from HCC across Europe, 17% in Japan, only 2% in China, and as much as 35% of black patients in Africa. This leads to the assumption that etiologic factors also have a role in the pathogenesis of this special type of liver carcinoma [8]. With all this in mind, this type of HCC is special not only histologically, but also clinically, and it is considered a separate clinical and pathological entity. Nowadays, the diagnosis of HCC can be made by radiologic criteria only (CT/MRI), by strictly following imaging protocols, even without a biopsy performed, if familiar and specific findings are established [11–14].

Conclusion

In conclusion, we can safely say that even though we have sophisticated medical imaging techniques and established criteria for the diagnosis of hepatocellular carcinoma, when it comes to nonspecific findings in extensive liver lesions, with a clinical presentation mimicking liver abscess, including long-term intermittent fever and persistent leukocytosis, one should always have in mind this special clinical and pathological entity.

References


