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CASE REPORT

Hepatocellular carcinoma associated to Behçet's disease

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Abstract: The occurrence of hepatocellular carcinoma (HCC) on a healthy liver is exceptional and represents a real diagnosis challenge for the clinician. Recently a particularly increased risk of cancer during Behçet's disease (BD) was reported by several studies. Only a few sporadic cases of liver cancer associated with this vascultis have been reported. We report an original observation of non-fibrolamellar HCC occurring on healthy liver in a Tunisian patient followed for BD. A 43-year-old man, followed since the age of 25 for BD with isolated cutaneous and mucosal involvement, and treated by colchicine, was admitted for exploration of a pain of the right hypochondrium evolving since a few months associated with an important slimming, anorexia, and evening fever. The clinical examination noted a firm and painful hepatomegaly. Radiological exploration (ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI)) showed a bulky hepatic tumor with highly developed arterial blood supply. Ultrasound-guided biopsy concluded at HCC without signs of fibrolamellar type or cirrhosis. Biological tests were without abnormalities and specific investigations eliminated underlying chronic hepatopathy (chronic viral hepatitis B or C, hemochromatosis, Wilson's disease or autoimmune hepatitis). The patient was treated symptomatically given the advanced stage of cancer. He quickly died after a month because of a multi-organ failure. HCC on healthy liver is exceptional and BD was suggested as a possible contributing factor. Thus, regular radiological monitoring seems to be recommended in any patient followed for BD, especially those with hepatic veins thrombosis.

Keywords: liver cancer, Behçet's disease, hepatocellular carcinoma, vasculitis, non-cirrhotic liver

1 Introduction

Hepatocellular carcinoma (HCC) occurs in more than 80% of cases in pre-existing liver injury (cirrhosis or other chronic non-cirrhotic liver disease)[1,2]. Rare cases can develop on previously healthy liver; specifically fibrolamellar carcinoma[3]. Apart from this particular histological type, chronic hepatitis C (CHC) on healthy liver remains exceptional[4,5].

Behçet's disease (BD) is a non-specific systemic vasculitis that is particularly common in young people around the Mediterranean and the old Silk Road[6]. Recently a particularly increased risk of cancer during this disease was reported by several studies[6–8]: standardized incidence ratio (SIR) at 2.13-3.10[9] and Hazard Ratio (HR) at 1.134[10].

Only a few sporadic cases of liver cancer associated with BD have been reported[9–13], and in large series like the South Korean series of 14,137 patients with BD, the frequency of HCC did not exceed 0.20%[10].

We report an original observation of non-fibrolamellar HCC occurring on healthy liver in a Tunisian patient followed for BD.

2 Observation

43-year-old man, followed since the age of 25 for BD with isolated cutaneous and mucosal involvement (recurrent oral ulcers, genital ulcers, pseudo-necrotic folliculitis, positive Pathery-test, and positive HLA B51), and treated by colchicine, was admitted for exploration of a pain of the right hypochondrium evolving since a few months associated with an important slimming, anorexia, and evening fever.

The clinical examination noted a firm and painful hepatomegaly. Abdominal ultrasound showed a round, heterogeneous tumor, measuring about 10 cm long axis, and developed at the expense of left lobe of the liver (Figure 1). Abdominal CT confirmed these findings and objectified the significant arterial blood supply of this tumor (Figure 2 and Figure 3). This tumor compresses the right portal vein without signs of thrombosis or loco-

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regional extension. There was no intra-abdominal lymphadenopathy, ascites, direct or indirect signs of cirrhosis or portal hypertension.

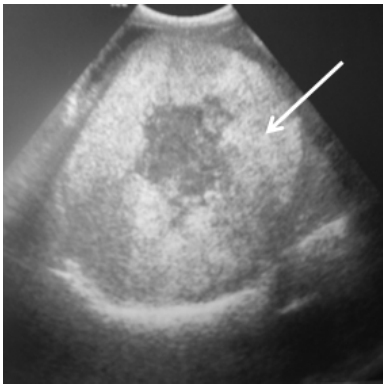

Figure 1. Abdominal ultrasound: Bulky heterogeneous tumor of the left lobe of the liver

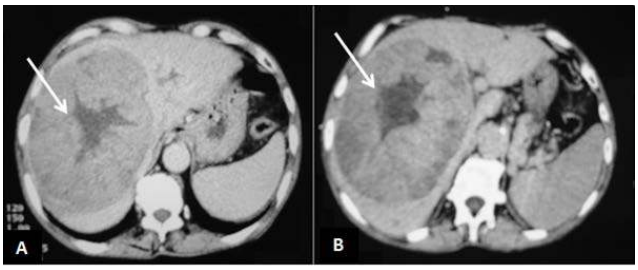

Figure 2. Axial abdominal CT without contrast injection (hepatic dome (A) and hepatic hilum (B) sections): large and heterogeneous liver tumor with central scar

Nuclear Magnetic Resonance Imaging (MRI) revealed a well-limited, encapsulated mass of heterogeneous signal with a central hyposignal scar on T1, hypersignal on T2, and unmodified signal after gadolinium injection. The peripheral region of the mass has a T1 intermediate signal, T2 heterogeneous hyposignal, and a heterogeneous contrast enhancement (Figure 4 and Figure 5).

The echo-guided biopsy puncture concluded with HCC. No characteristic signs of fibrolamellar carcinoma were noted.

The biological assessment, in particular transaminases, prothrombin rate, factor V of the hemostasis, gamma-glutamyl transferases, lactecodehydrogenases, electrophoresis and immunoelectrophoresis of serum proteins, and the alpha fto-protein, was without abnormalities. The serologies of viral hepatitis B and C were also negative. Serum iron, cupremia, cupruria, serum ceruloplasmin, and immunological status (antinuclear antibodies, anti-Liver kidney microsome type 1 antibodies, anti-mitochondrial M2 antibodies, and anti-smooth muscle antibodies) were within normal limits, thus eliminating underlying chronic hepatopathy (chronic viral

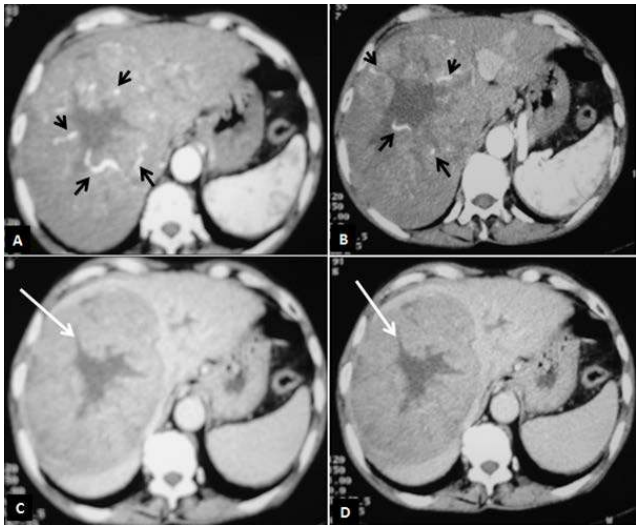

Figure 3. Axial abdominal CT with contrast injection (different vascular times: early arterial (A), late arterial (B), hepatic (C), and delayed phase (D)): heterogeneous aspect of the liver tumor (white arrow) with significant arterial blood supply (black arrows)

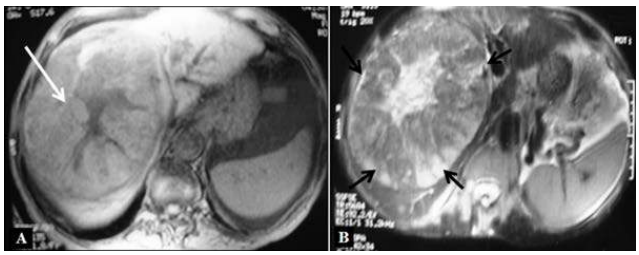

Figure 4. T1-weighted without contrast (A) and T2-weighted (B) axial hepatic MRI: heterogeneous aspect of hepatic mass (white arrow) with extensive arterial vascularization (black arrows)

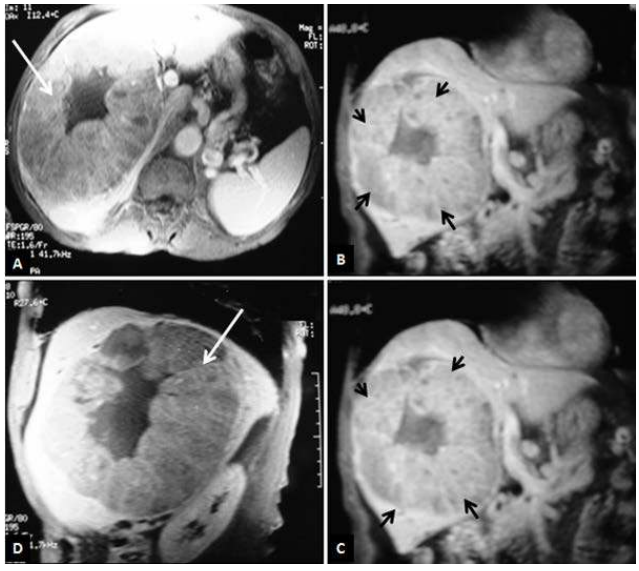

Figure 5. 3D T1-weighted hepatic MRI with contrast injection (different vascular times: early arterial (A), late arterial (B), late portal (C), and delayed phase (D)): heterogeneous aspect of the hepatic tumor (white arrow) with extensive arterial blood supply (black arrows)

hepatitis B or C, hemochromatosis, Wilson's disease or autoimmune hepatitis).

The patient was treated symptomatically given the advanced stage of cancer. He quickly died after a month because of a multi-organ failure.

3 Discussion

The development of HCC on previously healthy liver is exceptional[5]. This eventuality represented only 0.32% in the largest series of Giannini EG *et al.* of 3,027 cases of HCC[14].

Diagnosis is based, according to global recommendations, on the combination of medical imaging and histology[2,15,16]. The radiological aspects are very suggestive of the diagnosis. Ultrasound and CT presentations are the same as those of HCC on cirrhotic liver; size greater than 2 cm and intense arterial vascularization are very suggestive of the diagnosis[2,17].

MRI is considered superior to all other medical imaging techniques: ultrasonography, CT and positron emission tomography (PET-scan) for the diagnosis of focal liver injury[1,16,18]. The MRI aspect, especially on the T1, T2, diffusion, and sequences with gadolenate dimeglumine (Gadobenate dimeglumine-BenzylOxy-Propion -ic Tetraacetic Acid (Gd-BOPTA)) or gadoxetic acid (Gadolinium-EthOxyBenzyl-Diethylene Triamine Pentaacetic Acid (Gd-EOB-DTPA)) is the most specific of HCC on healthy liver[1,16,18].

HCC incidence increases with age, and the maximum of cases is diagnosed around the age of 70[1]. The young age of our patient would be another argument in favor of the promoting role of BD in the genesis of this liver cancer.

Indeed, the risk of any cancer during BD was significantly higher in the multiple nationalwide population-based studies compared to the general population: standardized incidence ratio (SIR) was 3.10 in men and 2.13 in women with BD in Jung YS *et al.* series[9], SIR was 1.5 in all patients and 1.8 in female patients with BD in Wang LH *et al.* study[19], and Hazard Ratio (HR) was 1.134 in Na SJ *et al.* series[10].

However, liver cancer remains exceptional in BD: 2 patients out of 512 with BD in the Turkish series of Bayraktar Y *et al.* (0.39%)[20] and 22 patients among 14,137 in the Korean series of Na SJ *et al.* (0.20%)[10]. The majority of cases were hepatocellular carcinoma[9–12], more rarely other types of liver cancer were reported: malignant hepatoma[12] and liver leiomyosarcoma[13].

The risk of elevated hepatic carcinogenesis associated with BD was confirmed by the Korean national study of Jung YS *et al.*, where SIR to develop hepatic cancer during this disease was equal to 4.00 compared to the general population[9].

The exact mechanism promoting carcinogenesis associated with BD is still unclear. It appears to be multifactorial involving persistent chronic inflammation, immune dysfunction, vasculitis, and some immunosuppressive therapies used in this disease[6,8–10,20].

For HCC, thrombosis of the hepatic veins may also be a possible contributory factor[20]. BD is known to be a condition with very high thrombogenic risk, and hepatic veins are often affected during this vasculitis[21].

No data were found in the literature regarding the clinical peculiarity of HCC in BD (incidence of ascites, portal vein hypertension, *etc.*); These data are difficult to specify because BD is also associated with a high risk of thromboembolism explaining the frequency of thrombosis of portal veins and portal hypertension even outside HCC[21]. Similarly, ascites can be part of the particular digestive involvement of this disease (entero-Behçet), regardless of the existence or not of an associated HCC[6,8–10,20].

Similarly, no specific recommendations have been found in the world literature concerning the periodicity of the clinical and radiological monitoring of these patients.

4 Conclusion

HCC on healthy liver is exceptional and BD was suggested as a possible contributing factor. Regular radiological monitoring (hepatic ultrasonography) thus seems to be recommended in any patient followed for BD in order to diagnose early hepatic degeneration. Subjects with BD with thromboembolic complications, particularly thrombosis of the hepatic veins, appear to have a significantly higher risk of developing liver cancer.

Conflicts of interest

The authors declare that they have no conflict interest.

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