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Unclassified Hepatic Hepatocellular Adenoma in Men Still A Diagnosis by Exclusion: Case Report and Review of the Literature

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Abstract:- Unclassified hepatic hepatocellular adenoma in men is still a challenging entity regarding clinical manifestations, diagnosis, and treatment as in our case. It still need more investigations determining their characteristics, risk of complications and malignant transformation in order to improve their therapeutic care.

Keywords:- *Unclassified hepatocellular adenoma, Liver resection, Management, Case report.*

I. INTRODUCTION

Unclassified hepatic hepatocellular adenoma in men is still a challenging entity regarding clinical manifestations, diagnosis, and treatment [1]. It constitutes a not well-defined hepatic adenoma subtype [1].

The aim of this case report and the literature review was to focus upon this rare tumor in order to improveits therapeutic care. The work has been reported in line with SCARE criteria [2].

II. CASE REPORT

A 17-years old man, with a personal history of appendectomy in 2019 via McBurney's incision. No familial medical history was noticed. He complainedabout a right abdominal pain lasting for few months. No use of steroids was related. Physical examination revealed a tender oblong-shaped mass, located in the right abdomen, mobile with breathing. It was 11 cm in diameter. His body mass index was 21.2 kg/m^2. Blood tests were within normal ranges especially alpha foeto-protein, cancer antigen 19-9,and carcino-embryonic antigen. Abdominal ultrasound showed a heterogenous isoechoicmass of the segment 5with an exophytic growth. Abdominal computed tomography revealed the existence of three lesions localized in segments 8,6, and 5. These lesions were 5, 2, and 11 cm in diameter respectively. These masses were heterogenous isodense spontaneously with slight contrast up take at the arterial phase and becoming iso-dense at portal and late phases (Figure 1). Magnetic resonance imaging demonstrated an exophytic lesion with a heterogenic signal (Figure 2). Its center has a hypersignal in T2 phase and a hyposignal in T1 signal without a significant contrast uptake at delayed phase. The other lesions localized in segments 8 and 6 showed hyposignal T2-weignted sequences, isosignal T1-weignted sequences, and a signal drop for in phase and out of phase sequences. Slight intake of contrast was described at the late phase.

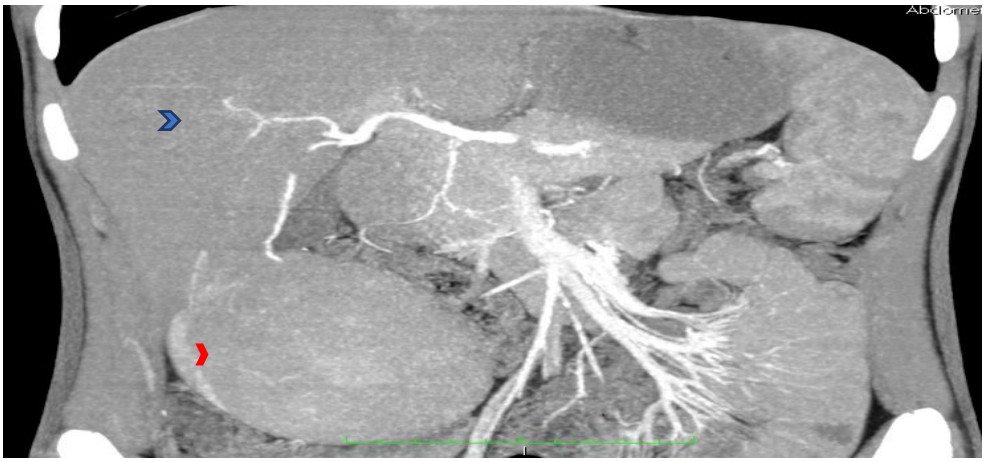

Fig. 1: Computed tomography reconstructions showing the two largest lesions. One lesion of 11 cm in diameter exophytic (red arrow) located in segment 5 and close to the middle hepatic vein. The other lesion was located in segment 8 close to portal veins (blue arrow)

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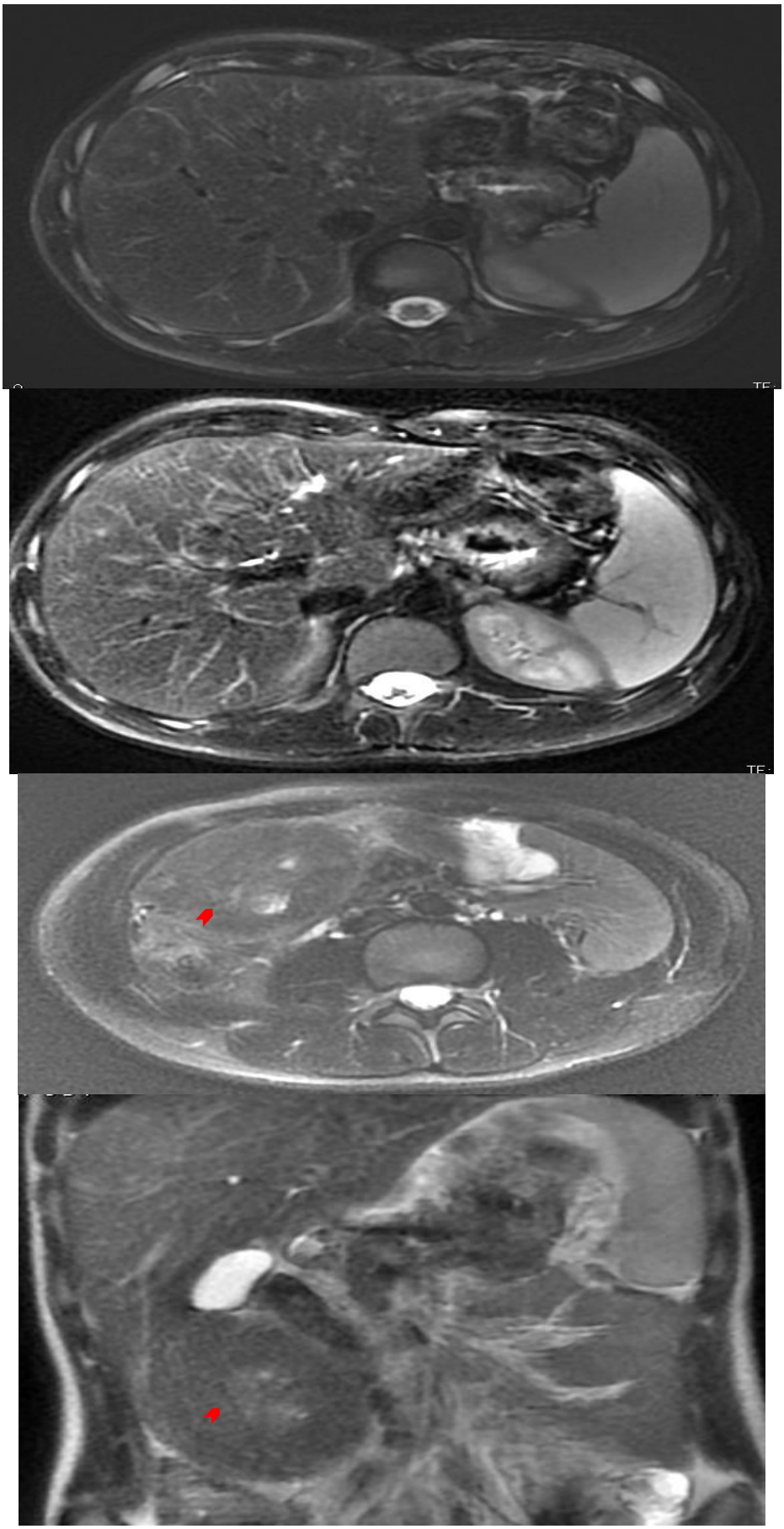

Fig. 2: Magnetic resonance imaging at T2-weignted sequences demonstrating bleedingin the exophytic lesion (arrow) with slight contrast intake for the masses

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Since these radiological features weren't conclusive, a percutaneous biopsy was performed revealinga hepatocellular adenoma without precision of the subtype. No malignant signs were noticed.The surgical treatment was carried out because of the bleeding complication, the diameter above 5 cm, and the male gender. A Makuuchi incision was done. Per-operatively, eight lesions in the right hepatic lobe were noticed (Figure 3). A right hepatectomy was carried on in two stages because the future remanent liver was insufficient. The first stage corresponded to a wedge resection of the exophytic lesion since it was bleeding with a right portal vein ligation and alcoholization (Figure 4).

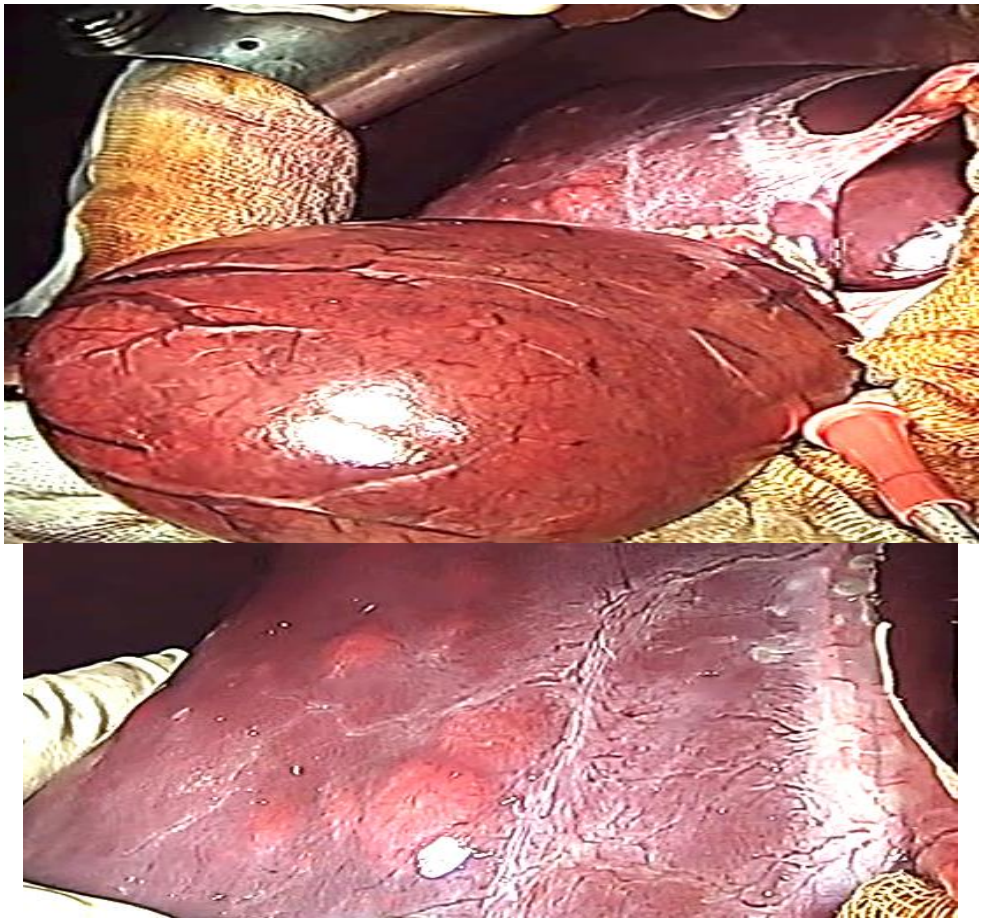

Fig. 3 : Per-operative vue revealing the existence of eightlesions: the three described by radiological imaging and five others superficial, with diameters of 1-2 cm located in the right hepatic lobe

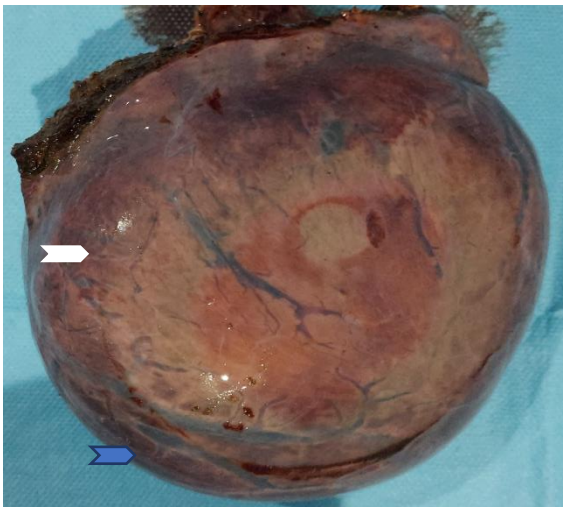

Fig. 4: Per-operative view of the exophytic lesion after resection. Notice the hypervascularization (white arrow) and the bleeding (blue arrow)

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The postoperative course was uneventful. A computed tomography performed one month after the second stage demonstrated a sufficient hypertrophy of the remaining liver over 1% of the corporal weight allowing the performance of the right hepatectomy. The histopathological exam with immunochemistry staining concluded to unclassified hepatocellular adenoma. No malignant signs were described. No relapse was noticed after a close follow-up at the outpatient department.

III. DISCUSSION

Our case illustrated an exceptional benign tumor in male gender referred as unclassified hepatocellular adenoma[1].It demonstrated fourparticularities. Firstly, no risk factors were reported for this young man. Secondly, the diagnosis was challenging requiring percutaneous biopsy since radiological features weren't able to differentiate this tumor from other liver tumors in one hand and from the other hepatocellular adenoma subtypes.Thirdly, MRI didn't diagnose all the present lesions leading to per-operative strategy modification and a challenging postoperative surveillance. Lastly, surgical indication wasthe bleeding complication for the exophytic lesion as well as the malignant transformation riskdue to male gender, exophytic growth, and size of the largest tumor above 5 cm.

Unclassified hepatocellular adenoma accounted for 5 to 10% of all hepatocellular adenomas [3,4].It occurred in non-cirrhotic livers [5]. As in our case, non-specific abdominal pain constituted a revealing circumstance [5]. Elsewhere, clinical manifestations varied from the absence of clinical signs in 50% casesto acute symptoms due to tumor rupture or bleeding [5,6].

Unclassified hepatocellular adenomawas characterized by the absence of mutations and specific mRNA as molecular definition which translated into the absence of risk factors, specific clinical manifestations, histopathological aspects, and immune staining [4,7]. Thus, it is stilla diagnosis by exclusion. Unlike women in whom oral contraceptives where incriminated for the development of hepatocellular adenomas, in men several factors where reported: metabolic syndrome, glycogen storage disease type 1a, familial adenomatous polyposis,and exposure to androgens[8].These factors varied according to hepatocellular adenoma subtypes. In fact, female gender, obesity, diabetes mellitus, and hepatic steatosis were encountered in inflammatory hepatocellular adenoma representing 40-50% cases [4]. Female gender with oral contraceptives intake were associated to hepatocyte nuclear factor-1-alpha-mutated hepatocellular adenoma [4]. This subtype accounted for 30-40% cases [4]. In regards toß-catenin-mutated hepatocellular adenomaand unclassified hepatocellular adenoma, male gender constituted a predictive factor[4]. It was associated to glycogen storage disease, androgen use, and familial adenomatous polyposis for ß-catenin-mutated hepatocellular adenoma encountered in 10-20% cases [4].

Unclassified hepatocellular adenoma ethiopathogeny is still not well understood [4,7] while it was well established for the other subtypes: IL6/JAK/STAT pathway activating mutations, inactive biallelic mutations of hepatocyte nuclear factor 1α, and β-catenin mutations forinflammatory hepatocellular adenoma, hepatocyte nuclear factor-1-alpha-mutated hepatocellular adenoma, and ß-catenin-mutated hepatocellular adenoma respectively [9].More recent subtypes were described: β-catenin-mutated hepatocellular adenoma exon 3, β-catenin-mutated hepatocellular adenoma exon 7-8, and sonic hedgehog-activated tumor. Hence, six subgroups have been determined so far and counting [10]. The latter constituted 5% of hepatic adenomas and 50% of unclassified subtype [11]. It was characterized by somatic fusion of inhibin beta E subunit and GLI1 responsible for GLI1 overexpression [11].

These mutations translated into radiological and histopathological features allowing in one hand the differentiation of hepatic adenoma from other liver tumors and in the other hand to distinguish between the hepatic adenoma subtypes. Since the risk of complications and malignant transformation depended on the subtypeof hepatocellular adenoma and guided the treatment modalities, reliable radiological features were needed. Magnetic resonance imaging with hepatobiliary contrast constituted the most sensitive radiological tool [12]. Hyperintensity on T2-weighted images associated with atoll sign was in favor of inflammatory hepatocellular adenoma with an area under the curve, a sensitivity, and a specificity of 0.953, 85-88%, and 88-100% respectively [13]. Intra-tumoral fat was observed in 17% cases [14]. It was focally distributed versus a diffuse distribution for hepatocyte nuclear factor-1-alpha-mutated hepatocellular adenoma [14] as well ashypointensityassociated to steatosis with an area under the curve of 0,957 [14]. Hyperintensity along with central scar was in favor of ß-catenin-mutated hepatocellular adenoma with an area under the curve of 0,903 [14]. In front of doubtful diagnosis, percutaneous biopsy may be useful as in our case [15]. In disagreement with the literature, magnetic resonance imaging was unable to bring out numerous superficial lesions in the right hepatic lobe for our case may be secondary to the superficial localization and the small size. This multifocality was reported in 20 to 50% cases [11].

The described radiological features corresponded to histopathological characteristics allowing to differentiate between the subtypes. For the unclassified subtype, no clear histological and immunohistochemical staining were observed [16] while the overexpression of serum amyloid A, the lack of liver fatty acid-binding protein, and C-reactive protein, as well as the diffuse glutamine synthetase and nuclear β-catenin expressions were in favor of inflammatory hepatocellular adenoma, hepatocyte nuclear factor-1-alpha-mutated hepatocellular adenoma, and ß-catenin-mutated hepatocellular adenoma respectively [9]. Other markers may be needed in order to define a new subgroup arising from this still unclassified as the case reported with histological brown pigment deposition [16].

The high risk of malignant transformation especially in male gender led to proposing liver resection: 47% in male gender versus 4% in female gender [1]. The other predictive factors for malignant transformation were exogenous steroids prolonged intake, obesity, metabolic syndrome, a tumor size over 5 cm as in our case, type 1a glycogen storage disease, and beta-catenin activation in exon 3 [10,15]. Surgical resection is still a cornerstone for the treatment of such tumors especially in case of bleeding risk: diameter superior or equal to 3.5 cm, visualization of lesional arteries, left lateral liver location, and exophytic growth as for our case [17]. Laparoscopic resection is considered more and more as an alternative to laparotomy with equivalent results in terms of mortality, morbidity, and relapse [18].

As in our case, it can be life-threatening because of arterial bleeding reported in 20-40% cases especially in sonic hedghoge subtype [10]. Transarterial embolization may be carried out but can be challenging in case of several small feeding vessels [14]. Hence, surgery remained an effective treatment in such complications as in our patient [18].For non-complicated hepatocellular adenoma smaller than 5 cm, trans arterial embolization may constitute a mini-invasive alternative to surgery especially for young patients with cosmetic outcomes [19].

IV. CONCLUSIONS

Unclassified hepatocellular adenomas need more investigations determining their characteristics, risk of complications, and malignant transformation in order to improve their therapeutic care. It is still a diagnosis by exclusion.

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INFORMED CONSENT

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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