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An Unexpected Liver Tumor Finding During Multiorgan Harvesting: Steatohepatitis Matters

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Abstract

The burden of Non-Alcoholic Fatty Liver Disease (NAFLD) and Non-Alcoholic Steatohepatitis (NASH) are increasing worldwide. Growing evidences showed its ability to progress to Hepatocellular Carcinoma (HCC). In the transplant field, NAFLD is the most common cause of discarding the livers and, to further complicates matters, the high prevalence of NAFLD-associated HCC in the absence of cirrhosis could be a factor jeopardizing the complex transplant chain. Up to now, specific recommendations for HCC surveillance in these patients are not available but, transplant process, could be a high-risk setting to be urgently addressed. Here we report the case of an organ donor in whom, at the time of laparotomy, an unexpected NAFLD associated HCC was found thus significantly impacting the complex transplant chain. This case is described to reflect on the impact of NAFLD on donor population, and on logistic issues in the transplant process.

Keywords: Steatohepatitis; Donor HCC; Liver transplantation.

Abbreviations: BMI: Body Mass Index; CIT: Cold Ischemia Time; CT-SCAN: Computed Tomography; HCC: Hepatocellular Carcinoma; HGDN: High Grade Dysplastic Nodule; LGDN: Low Grade Dysplastic Nodule; LRN: Large Regenerative Nodules; LT: Liver Transplantation; MP: Machine Perfusion; MRI: Magnetic Resonance Imaging; NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; WIT: Warm Ischemia Time.

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Introduction

Liver graft steatosis is commonly founded during procurement and it is the main reason to discard a liver graft [1]. Steatotic livers are considered suboptimal grafts in LT, as they are more prone to develop a higher rate of ischemia-reperfusion injury, primary non-function and graft dysfunction [2]. Non-Alcoholic Fatty Liver Disease (NAFLD) is now the most common chronic liver disorder in Western countries and, affecting nearly 25% of adult population, it is placing significant burden on healthcare systems worldwide [3]. This liver disease represents the hepatic mirror of metabolic syndrome and encompasses different clinical-pathological spectrum of liver disease: Simple steatosis (NAFLD), Non-Alcoholic Steatohepatitis (NASH) and cirrhosis. Its prevalence is expected to rise significantly in next years in parallel with the dysmetabolic epidemics (diabetes and obesity). Recently, NAFLD has been identified as the most growing causes of HCC in the absence of cirrhosis [4]. Its ability to develops HCC bypassing the cirrhotic stage is reported to be significantly higher in respect to general population reaching nearly 40% in some studies [5] and this would represent a great public health challenge in terms of surveillance programs. Recently, the European Association for the Study of the Liver (EASL) addressed an open letter to the European Parliament asking to improve liver cancer screening in patients with underlying risk factors including those with NAFLD [6]. Current scientific evidences are lacking to build up large scale surveillance indications [7] but, specific high risk area, as transplant setting is, must be accordingly managed.

Here we describe a case of 55-year-old organ donor who was unexpectedly diagnosed with HCC on the background of undiagnosed NASH during liver retrieval. This case is reported to track the intricate matter of NAFLD nowadays in the transplant world.

Case report

A 55-year-old organ donor who experienced a cerebral hemorrhage due to a polytrauma was identified as a potential organ donor on May 2020. This man resulted vaccinated for HBV hepatitis and the past medical history was collected from the family. No clear specific risks for HBV, HCV and HIV and prion disease raised. His BMI was 33, waist circumference was 105 cm and on clinical laboratory examinations, he had hypercholesterolemia with HDL cholesterol < 40 mg/dl. Glycaemia was 140 mg/dl while liver function tests were normal. Abdominal ultrasound revealed a slight inhomogeneous liver texture with spleen diameter of 12 cm. Urgent CT SCAN revealed multiple bones fractures and contusions at the level of lungs and segments 5 to 8 of the liver. He was judged as a standard donor and no specific second opinion at National Transplant Level was required; thus, after family consent, the Regional Transplant Centre set up the organ donation procedure.

At liver transplant surgeon examination, the liver appeared enlarged and two nodules 14 and 8 mm respectively were noted at segment 2. Urgent pathological examination revealed a high-grade nodular dysplasia with borderline histomorphology and architectural characteristics, not allowing the exclusion of an initial progression towards a well-differentiated HCC. The smallest lesions were negative for neoplasia. Therefore, that liver was discarded and no other organs were retrieved from that donor. Subsequent definitive histological diagnosis on paraffined liver specimen confirmed the presence of borderline large cells High Grade Dysplastic Nodule (HGDN). Mixed findings were found: Diffuse multifocal CD34+ sinusoidal capillarization, CK7+ ductular reaction, pluricellular atypical hepatocytes chain, focal reticulin network depletion, membrane positivity of Beta-catenin as well as focal nuclear positivity in p53 antibody and the presence of aspects of “nodule in nodule” (Figure 1) without a clear transition from HGDN to overt HCC. Macro-vesicular steatosis was 20%, micro-vesicular 80% (Figure 2). Liver parenchyma examinations was in evolutive stage towards cirrhosis.

All the imaging was retrospectively reviewed by an HPB radi- ologist, knowing the pathology results of the biopsy. He couldn’t find out any liver lesion.

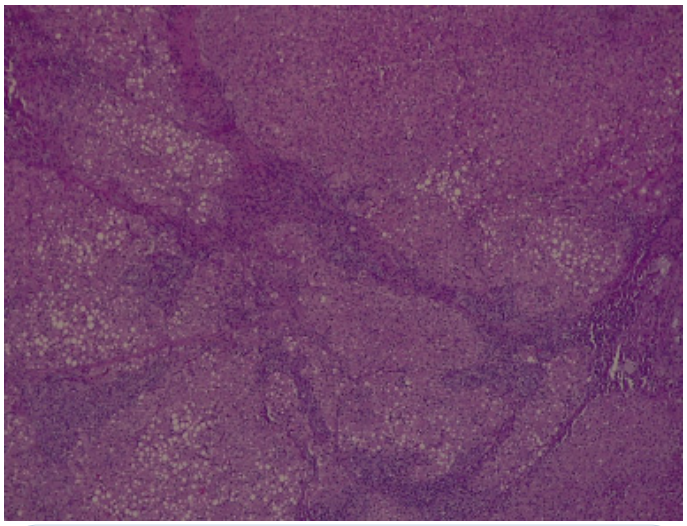

Figure 1: Hematoxylin and Eosin Stain 5-fold increase; dysplastic macronodule with subverted acinar architecture and “nodule in nodule” appearance.

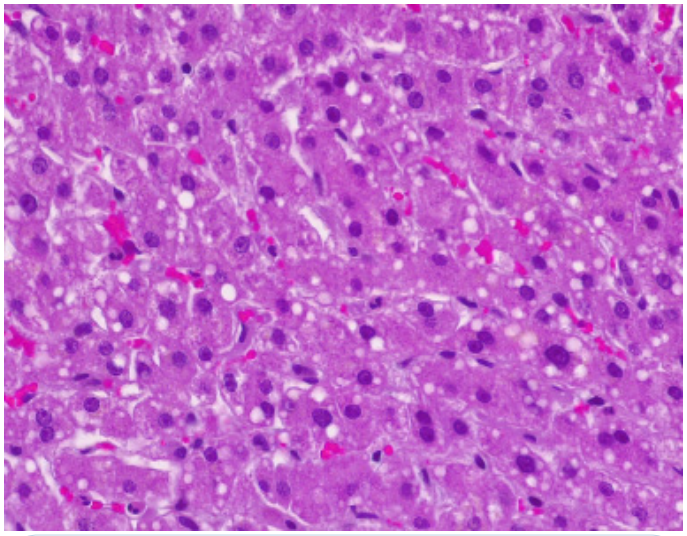

Figure 2: Hematoxylin and Eosin Stain 20-fold increase; liver tissue surrounding the nodule with prevalently micro-vesicular steatosis.

Discussion

NAFLD and HCC

Hepatocellular Carcinoma (HCC) is the most common malignancy of the liver and the fourth most common cause of cancer-related death worldwide. Hepatocellular carcinogenesis is a multistep process mirrored by the morphologic classification of cirrhotic lesions: Large Regenerative Nodules (LRN), Low Grade Dysplastic Nodules (LGDN), and HGDN. This latter entity is a neoplastic lesion belonging to the “borderline malignancy”

category and requiring accurate distinction from well-differentiated and early HCC [8]. HCC arises on the background of liver cirrhosis due to hepatitis B and C in up to 80% of the cases. However, in recent years a shift in underlying etiology towards environmental, dietary and lifestyle factors had been described to be linked with HCC [9]. Currently, NAFLD is one of the principal causes of chronic liver disease in the world. In western countries, in parallel with the increasing rate of obesity and diabetes, the prevalence of NAFLD is remarkable with a global prevalence of 25% of the population. NAFLD is mainly a benign disease but it may progress to NASH, in which simple steatosis is associated with inflammation, hepatocyte injury with or without fibrosis. Almost 3% to 6% of the US population resulted to be affected by NASH [10], but, in view of the epidemiological trends in the associated metabolic conditions and the diagnostic underestimation due to low liver biopsy propensity, NASH is expected to increase of 18% by 2030 [2].

In recent years, NAFLD has been identified as the most growing causes of HCC in the absence of cirrhosis [4]. NASH-associated HCC may develop either in presence either in absence of cirrhosis. Moreover, diabetes, one of the main constitute of metabolic syndrome, is demonstrated to be associated with a 2-3-fold increase in the risk of HCC, regardless of the presence of other major HCC risk factors [11].

The ability of NASH-HCC to bypass the cirrhotic stage is representing a great public health challenge in terms of screening programs. Liver Transplantation (LT) is another setting that will be affected at different levels form the NAFLD epidemics not only on the recipient perspective but also on the donor process management. Following the significant reduction in HCV epidemics due to availability of highly efficacious HCV direct acting antivirals [12], currently NAFLD/NASH is the second leading cause of Liver Transplantation (LT) in the US, increasing by 170% from 2004 to 2013 [13].

Moreover, NASH-HCC has been identified as the indication to LT with the steep increase of 7.7-fold (from 2.1% to 16%) in US liver transplant candidates [9,14-16].

Why steatotic graft matters?

Many liver donor boundaries have been safely pushed over in the last decades of liver transplant activity. Grafts from aged donors, or HCV cases, or DCD donors are now almost routinely used [17]. Liver graft steatosis still represents a warning aspect for liver transplantation as these grafts might compromise patient and graft survival [2,18,19]. It represents one of the main causes for discarding a grafts, reaching rate of 42% of all donor offers [20] and further compromising the gap between organs availability and liver demand.

So far, the main cut-off for accepting a steatotic graft has been a macro-vesicular steatosis of 30% [21]. While moderate (30-60%) macro-steatosis had been shown that it could be safely used in the absence of other risk factors (older donor age, low cold ischemia time, DCD grafts), a severe steatosis (>60%) has been classically considered a contraindication for LT. There is great scientific interest in extending this limit and it represent the main demand to the Machine Perfusion (MP) research.

It has been well established that this device can rescue many marginal grafts by oxygenating the grafts ex vivo and before im- planting them [22]. Very long cold ischemia time [CIT] or pro- longed donor Warm Ischemia Time (WIT) in DCD donation have been efficiently bypassed by MP and those grafts have been successfully implanted [23,24]. Literature regarding machine perfusion of steatotic livers is poor and mostly animals based. So far, defatting cocktails added to perfusion fluids during the MP cycle have been tested, showing a reduction up to 32% of the free radicals production. The intention is to decrease the triglyceride load, enhancing the lipolysis of the intracellular fat storage. This would decrease the Reactive Oxygen Species (ROS) production [20] and finally avoid the harmful effect of ischemia- reperfusion injury. Up now, these experimental studies were performed on pigs or rodent, therefore there is an urgent need of clinical models.

Pitfalls of the steatosis detection during liver organ donation

Organ retrieval process is a complex multidisciplinary chain usually progressing during few hours and in an acute emergency setting. Thus, careful identification of steatosis framework is not fully applicable. Liver Ultrasonography (US) is always part of the donor assessment and the detection of moderate-severe fatty liver (> 20%-30% steatosis) is similar to Computed Tomography (CT-SCAN) or Magnetic Resonance Imaging (MRI) with a sensitivity and specificity of 84.8% and 93.6% respectively, in respect to liver histology as reference standard [25]. However, the urgent setting in which US is performed during the donation process and the presence of gas or obesity as well as liver fibrosis may decrease its accuracy and applicability. Accordingly, biochemical scores for steatosis such as steatotest, HS index, and fatty liver index, are not routinely applied in the LT setting.

Body Mass Index (BMI), a simple and easily applicable test able to independently predict the presence of steatosis is always available in the donor data but is of limited use in clinical practice in view of the low sensibility. Nevertheless, an additional matter of issue relies on proper identification of the transition of NAFLD to NASH whose diagnosis requires a liver biopsy.

An additional issue raised from our case report. In a recent metnalysis which included 7 observational studies involving 3567 cases of HCC among 23059 subjects, the prevalence of HCC in non-cirrhotic NASH was 38% with an overall pooled estimation of threefold increase risk of HCC in respect to other etiologies (OR 2.61, 95% CI 1.27-5.35, p= 0.009 [26]. Thus, organ donor with stigmata of metabolic syndrome and US diagnosis of severe steatosis should undergo a dedicated CT SCAN, whenever possible, to exclude the presence of HCC.

How does a steatotic graft impact the transplant logistics?

Most of the research on steatotic grafts is concentrated in clinical field but no one has yet analyzed the logistic impact in the liver transplant activity from donation to the transplant. This case offers many discussion points.

Firstly, before the retrieval the steatosis was not well assessed as the pathologist did and the chain of transplant was set up as usual. The proper identification of NAFLD, a condition with a still low public awareness, is a critical issue as the related general medical picture (past medical history, dietary habit, alcohol and drug consumption) may not be always available in the donor information either due to the acute crisis related to sudden death and either due to the time-dependent examination (glycosylate hemoglobin etc .).

Secondly, the chain of the organ procurement and implantation was set up as usual. Not only retrieval team, but all the transplant teams, operating theatre staff, intensive care team

and the patient were all alerted uselessly. Because of the incidental HCC, the rest of the retrieved organs were not then implanted, therefore the inconvenience was multiplied for the number of organs retrieved. Definitely, these kinds of organ procurements are not cost-effective and sometime they are time consuming.

Conclusion

The high prevalence in general population of metabolic syndrome, steatosis and the more and more alarming data on the progression of NAFLD toward cancer should encourage the definition of specific pre-retrieval liver donor evaluation. Waiting for scientific evidences rigorously addressing specific HCC surveillance program for NAFLD patients, a reliable algorithm fitting the pre-retrieval organ procedures to accurately estimate the presence of NAFLD/NASH, assess macro-/micro-vesicular steatosis and the implementation of specific HCC screening through a well dedicated imaging are urgently awaited.

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