SUCCESSFUL MULTIMODAL MANAGEMENT OF A GIANT HEPATOCELLULAR CARCINOMA IN A NON- CIRRHOTIC LIVER: A CASE REPORT

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Abstract

Background: Hepatocellular carcinoma (HCC) found a in non-cirrhotic liver represents a minority of HCC cases and remains poorly studied. Due to its specific characteristics and evolution, this tumour requires a different management compared to HCC in a cirrhotic liver.

Case report: The authors describe the case of a 68-year-old man diagnosed with a large giant and only mildly symptomatic HCC in a non-cirrhotic liver. The 23 cm HCC was discovered when a thoracoabdominal computed tomography was performed following mild abdominal pain. After a multidisciplinary discussion the tumour was judged to be borderline, but potentially resectable after neoadjuvant therapy and preparation for surgery. The patient underwent selective internal radiation therapy radioembolization of the right hepatic artery lobe with 5,5 GBq of 90Y-labeled glass microspheres. It was followed by extended right hepatectomy after preparation by embolization of the right portal and the right hepatic veins. Thirty months after surgical resection the patient showed neither clinical, radiological nor biological signs of HCC recurrence.

Discussion: HCC in non-cirrhotic liver is less common than in cirrhotic liver but has a better prognosis, thanks to a greater opportunity for surgical resection. The symptoms often emerge late and are unspecific, thus delaying the HCC diagnosis. Advances in surgical resection by laparotomy or laparoscopy, and neoadjuvant therapy in preparation for surgery, have proven to be effective. However, high mortality persists due to late diagnosis linked to the inability of identifying groups at risk of HCC in the non-cirrhotic population and inadequate screening.

Keywords : Liver; cancer; transplantation; surgery; outcome; embolization.

Data availability statement: the data described in this manuscript can be requested by email to the corresponding author.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy (70-90% of cases) [1-4]. According to data from 2020, HCC is the sixth most common cancer and the third most deadly worldwide [5]. The 5-year overall survival rate for HCC is 18% [1]. However, if HCC is diagnosed at an early stage, allowing curative management, this rate may reach up to 50% [6]. HCC occurs in a non- cirrhotic liver (NCL) in only a minority of cases (5 to 20%) [1,2,7-10]. An HCC is defined as being "large" when its size exceeds 10 cm, and surgical resection is the only chance of a cure for large HCC in NCL. In this report, the authors describe the case of an incidental giant HCC in a NCL, and its successful multidisciplinary and multimodal management approach.

Case report

A 68-year-old man had developed unexplained lower abdominal pain and pruritus over several months. No other complaints were reported. His medical history included a prostate adenocarcinoma treated with surgery and radiotherapy, arterial hypertension, non-insulin-requiring type-2 diabetes, mild hypercholesterolemia, and previous smoking stopped 26 years ago. A gastroscopy performed 4 months earlier demonstrated grade B oesophagitis but did not show any signs of portal hypertension or gastropathy. The patient confirmed a habitual consumption of 20 glasses of alcoholic drinks per day.

The patient's blood test showed moderately elevated aspartate aminotransferase (ASAT: 96 U/L), alanine aminotransferase (ALAT: 43U/L) and gamma-glumatyl transferase (γGT: 137 U/L), in addition to a highly increased alpha-fetoprotein (AFP) level) (5,201 µg/mL; normal values < 8.8 µg/mL). No hepatitis virus infection was detected.

A thoracoabdominal contrast-enhanced computed tomography (CT) scanner revealed a 23 cm liver tumour undertaking almost the entire right hepatic lobe with a segment IV extension (Fig 1). It presented a radiological appearance of HCC with an enhancement in the arterial phase and a portal wash-out. Imaging revealed no adenopathy, ascites nor splenomegaly. No

secondary pulmonary or bone lesions were observed, and the liver did not showed signs of cirrhosis. Further assessment with 18 fluorodeoxyglucose positron tomography ([18F]FDG-PET/CT) demonstrated an increased 18F- FDG uptake by in the hepatic tumour without distant metastasis.

After discussion in a multidisciplinary oncology consultation, the lesion was considered as borderline due to close contact with the liver hilum structures and potentially small future liver remnant, but potentially resectable after neoadjuvant therapy and preparation for surgery. Consequently, the decision to carry out a multimodal management approach with a potentially curative aim was taken, combining radioembolization, followed by extended right hepatectomy with previous preparation with combined portal- and hepatic veins embolization. The patient underwent selective internal radiation therapy (SIRT) of the right hepatic lobe with 5,5 GBq of 90Y-labeled glass microspheres The radioembolization was performed with yttrium 90-loaded microbeads microspheres injected into the right hepatic artery under radiological control. This led to a decrease in AFP to 4,830 µg/mL and a reduction in the size of the liver lesion tumour down to 15 cm on CT scan (Fig 2). Volume of liver segments II and III (left lobe) was calculated at 558 cm3, 18% of the whole liver volume. Subsequently, embolization of the right portal vein (glue) (Fig 3) and the right and middle hepatic veins (plugs) was performed by the interventional radiology team to achieve the growth of the future left liver remnant (Fig 4). Four weeks after embolization, sufficient hypertrophy of segments II and III was obtained with a volume of the left lobectomy calculated at 1,096 cm3.

Two months later, after a further delay due to a SARS-CoV-2 infection, hypertrophy of segments II and III was obtained which permitted an extended right hepatectomy including segment IV, was performed by laparotomy (R0 resection with 2 cm margin, complete resection with negative lymph nodes). Anatomopathological analysis confirmed HCC at stage ypT1bN0M0. Neither fibrosis nor steatosis was described in the non- tumorous liver. At 30-month follow-up, the patient showed no signs of HCC recurrence either clinically, radiologically (thoraco- abdominal

CT scan) (Fig 5) or biologically (normal AFP level).

Discussion

Although the majority of HCCs occur in cirrhotic patients, between 5 and 20% of HCC cases develop in NCL [6,9]. The diagnosis of HCC in NCL is challenging and is often characterized by a slow and insidious progression. Similarly to the present case, it is usually diagnosed at an advanced stage when the considerable tumour burden makes the disease symptomatic [7,8]. Symptoms are non-specific at this point: abdominal pain, abdominal distension, and/or weight loss [7]. The delay in the diagnosis of HCC in NCL is due to the large liver reserve, the difficulty in targeting the population at risk and the lack of efficient and cost-effective screening methods [5-9].

Decision-making algorithms used in the choice of treatment for HCCs in cirrhotic liver (i.e. Barcelona Clinic Liver Cancer (BCLC) staging or the Milan criteria) are not relevant for patients with NCL [8,11]. The cornerstone of treatment for HCC in NCL is surgical resection, performed using laparotomy or laparoscopy [7,9,12]. In recent years laparoscopy has become the standard approach due to its comparable oncological results to laparotomy but fewer complications. However, it is not always feasible and remains recommended particularly if the HCC is small and has developed in the favourable liver segments (II, III, IVb, V and VI) [2,12]. When possible, anatomical resection, such as segmentectomy or lobectomy, is preferred from an oncological point of view. If not, a tumour resection with healthy margins of 2 cm reduces the risk of recurrence [2]. If the resection is complete, it offers postoperative survival rates of 96%, 87% and 68% at 1, 3 and 5 years, respectively (in patients without vascular invasion) [7], thanks to the preserved liver function allowing extensive and complex procedures [10,11]. In order to limit the risk of post-operative liver failure due to the extensive resection, it is necessary to assess the volume and/or the function of the future liver remnant. These are calculated using computer modelling programs based on thoracoabdominal CT scan or Magnetic Resonance Imaging (MRI). Literature highlights the necessity to preoperatively ensure a residual liver

volume equivalent to at least 25-30% of the initial total volume of a healthy liver [12]. Despite the low perioperative mortality rate, the close vascular and anatomical relationships of HCC impose extreme caution during surgery [10].Therefore, it is essential to localise the tumour and clarify its relationships with adjacent structures before any surgical approach [12]. In light of the regenerative capacities of NCL, liver resections can be repeated in the event of HCC recurrence [7,13].

Various neoadjuvant treatments can be considered in the preparation of patients for surgery and to perform extended resections, as in this case. Some, such as chemoembolization, allow the progression of the tumour to be controlled and even to regress in size [2,7]. Others, such as portal embolization (alone or associated with embolization of the hepatic veins) or associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), induce hypertrophy of the contralateral liver lobe. Radioembolization, on the other hand, combines regression of tumour size with hypertrophy of the contralateral liver lobe [12]. Portal embolization is usually the first option for patients with an estimated small residual liver volume [11,12]. As in the presented case, it can be combined with hepatic venous embolization to optimize the hypertrophy effect [14, 15].

Unlike HCC in cirrhotic liver meeting the Milan criteria (one nodule ≤ 5.0cm or ≤ 3 nodules ≤ 3.0cm, without vascular invasion) [11,16], liver transplantation is rarely indicated in HCC in NCL [7, 17]. Indeed, although it permits treatment of both HCC and possible underlying liver pathology, it does not offer a higher survival rate than resection and has additional disadvantages: long waiting time due to organ shortage and higher operative and postoperative risks (related to immunosuppressant use) [2,10,12]. However, it is recommended for unresectable HCC, HCC with a high risk of recurrence, or intrahepatic recurrence after hepatectomy, in patients without macrovascular invasion or extrahepatic spread [7,10,12].

Among other treatment options, systemic chemotherapy is not very effective on HCC cells and may be used as palliative treatment [7-10,13]. New molecules (chemotherapy, immunotherapy,

targeted therapy) to improve the survival of patients with unresectable HCC are currently under investigation. One of the main causes of mortality in HCC in NCL is recurrence after curative treatment [7,13]. According to Chiche et al [13], post-resection recurrence of HCC in NCL is predominantly intra-hepatic and occurs in 24.1% of cases during the first year and 31.5% of cases after 5 years. The survival rate continues to decrease after this 5-year limit due to late recurrence, reaching 36.7% at 10 years [13]. Long-term post- operative surveillance seems therefore essential [10,13]. There are no established recommendations yet, but Chiche et al [13] proposed that all patients should be followed up every 4 months for the first year after surgery and subsequently twice a year for 3 years. If one or more predictive factors for recurrence are present, twice- yearly follow-up should be maintained for 10 years. If this is not the case, then follow-up may be spaced out to once a year but paying particular attention to the liver as the majority of late recurrences are intrahepatic.

Comments of Figures

Figure 1: Abdominal computed tomography (axial planes) revealing a 23 cm hepatocellular carcinoma in the right liver lobe, with segment IV extension and contact with the liver hilum and the portal vein division;

Figure 2: Abdominal computed tomography (axial planes) performed after radioembolization, confirming the decreased size of the tumour, measured at 15 cm;

Figure 3: Percutaneous portal vein angiography (A) and embolization of the right branch of the portal vein (B);

Figure 4: Abdominal computed tomography (A: coronal plane; B: axial plane) performed 6 weeks after combined portal and hepatic vein embolization demonstrating the contrasted glue (right portal veins) and the plugs (right and middle hepatic vein) (white arrows);

Figure 5: Abdominal computed tomography (axial plane) performed at 2-year follow-up showing the absence of HCC recurrence and hypertrophy of the left liver.

References

[1] Villanueva A. Hepatocellular carcinoma. N Engl J Med. 2019;380(15):1450-1462.

[2] Detry O, Troisfontaine F, Meurisse N, et al. Prise en charge multidisciplinaire des tumeurs malignes primitives du foie. Rev Med Liege. 2021;76(5-6):519-524.

[3] Chedid MF, Kruel CRP, Pinto MA, et al. Hepatocellular carcinoma: diagnosis and operative management. Arq Bras Cir Dig. 2017;30(4):272-278.

[4] Marengo A, Rosso C, Bugianesi E. Liver cancer: connections with obesity, fatty liver, and cirrhosis. Annu Rev Med. 2016;67:103-117.

[5] International Agency for Research on Cancer. GLOBOCAN 2020: Estimated number of incident cases and deaths of cancer in 2020, worldwide, both sexes, all ages. Lyon: International Agency for Research on Cancer. https://gco.iarc.fr/today/home. Accessed September 25, 2021.

[6] Tempia-Caliera AA, Ksontini R, Moradpour D, Denys A, Halkic N. Le carcinome hépatocellulaire: une approche multidisciplinaire [Hepatocellular carcinoma: a multidisciplinary approach]. Rev Med Suisse. 2005;1(24):1621-1629.

[7] Desai A, Sandhu S, Lai JP, Sandhu DS. Hepatocellular carcinoma in non-cirrhotic liver: A comprehensive review. World J Hepatol. 2019;11(1):1-18.

[8] Schütte K, Schulz C, Poranzke J, et al. Characterization and prognosis of patients with hepatocellular carcinoma (HCC) in the non-cirrhotic liver. BMC Gastroenterol. 2014;14:117.

[9] Zhang Y, Wang C, Xu H, Xiao P, Gao Y. Hepatocellular carcinoma in the noncirrhotic liver: a literature review. Eur J Gastroenterol Hepatol. 2019;31(7):743-748.

[10] Alkofer B, Lepennec V, Chiche L. Hepatocellular cancer in the non-cirrhotic liver. J Visc Surg. 2011;148(1):3-11.

[11] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182-236.

[12] Allaire M, Goumard C, Lim C, Le Cleach A, Wagner M, Scatton O. New frontiers in liver resection for hepatocellular carcinoma. JHEP Rep. 2020;2(4):100-134.

[13] Chiche L, Menahem B, Bazille C, et al. Recurrence of hepatocellular carcinoma in noncirrhotic liver after hepatectomy. World J Surg. 2013;37(10):2410-2418.

[14] Heil J, Korenblik R, Heid F et al. Preoperative portal vein or portal and hepatic vein embolization: DRAGON collaborative group analysis. Br J Surg. 2021; 108(7): 834-841.

[15] Korenblik R, van Zon JF, Olij B et al. Resectability of bilobar liver tumours after simultaneous portal vein embolization versus portal vein embolization alone: meta-analysis. BJS Open. 2022; 6(6): zrac141.2.

[16] Schielke A, Meurisse N, Lamproye A et al. Selection criteria for liver transplantation in patients with hepatocellular carcinoma. Eastern and Western experiences, and perspective for the future. Acta Gastroenterol Belg. 2019; 82 (2): 314-318.

[17] Mergenthal H, Adam R, Ericzon BG et al. Liver transplantation for unresectable hepatocellular carcinoma in normal livers. J Hepatol 2012; 57(2): 297-305.