Brazilian Journal of TRANSPLANTATION

https://doi.org/10.53855/bjt.v27i1.584_ENG

CASE REPORT

Thyroid Metastases from Hepatocellular Carcinoma after Liver Transplantation

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Seccion editor: Ilka de Fátima Santana F. Boin

Received: Mar. 15, 2024 | Approved: Sept. 08, 2024

ABSTRACT

Hepatocellular carcinoma (HCC) patients with metastases to the thyroid are extremely rare. A patient who underwent liver transplantation for HCC recurrence had metastatic thyroid recurrence detected 4 years later. A literature review identified six documented cases, analyzing relevant data on HCC with thyroid metastasis following liver transplantation. There is a prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) as etiologies of liver disease (83.3%), with alpha-fetoprotein (AFP) levels elevated in five cases. Additionally, the time between the diagnosis of HCC and thyroid metastasis was within 3 years. The patient remains clinically stable in outpatient follow-up, with an 8-month current survival after total thyroidectomy.

Descriptors: Hepatocellular Carcinoma; Neoplasm Metastasis, Thyroid Neoplasms.

Metástase Tireoidiana de Carcinoma Hepatocelular após Transplante Hepático

RESUMO

Pacientes com metástase tireoidiana de carcinoma hepatocelular (CHC) são extremamente raros. Um paciente que realizou transplante hepático devido à recorrência de CHC apresentou metástase tireoidiana detectada 4 anos depois. A revisão de literatura identificou seis casos documentados, analisando informações relevantes sobre CHC com metástase tireoidiana após transplante de fígado. Verificou-se a prevalência do vírus da hepatite B (VHB) e da hepatite C (VHC) como etiologias da doença hepática (83,3%), com níveis elevados de alfafetoproteína (AFP) em cinco casos. Além disso, o tempo entre o diagnóstico de CHC e a metástase tireoidiana foi inferior a 3 anos. O paciente permanece clinicamente estável no acompanhamento ambulatorial, com sobrevida atual de 8 meses após tireoidectomia total.

Descritores: Carcinoma Hepatocelular; Metástase Neoplástica; Neoplasias da Glândula Tireoide.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver, with an annual worldwide incidence of approximately 500,000-1,000,000 cases, resulting in at least 700,000 deaths per year.[1] More than 80% of HCC cases are associated with hepatitis B virus (HBV) and hepatitis C virus (HCV), making it a prevalent complication and one of the main causes of death in compensated cirrhotic patients.[2] Liver transplant (LT) is a treatment modality for HCC. Although the recurrence of HCC after liver transplantation is the main obstacle to the success of this treatment, described in the literature between 8 and 30%[3], metastases to the thyroid are extremely rare, being documented in only eight studies. Two possible mechanisms responsible for the low incidence of thyroid metastases are the challenges that cancer cells face in adhering to the thyroid. These challenges are due to rapid arterial flow and the inhibitory effects of high oxygen saturation and iodine concentrations in the gland, which restrict malignant tumor growth.[4] The anatomy of venous return from the neck may also contribute to the low incidence.[5]

MATERIAL AND METHODS

A search and analysis of the literature were conducted in the PubMed (www.pubmed.gov) and SciELO-Brazil databases for all articles containing the terms "thyroid metastases from hepatocellular carcinoma," "metastasis of liver cancer to the thyroid," and "thyroid metastases in a patient with hepatocellular carcinoma". In total, eight studies were identified, and data from six were included in the analysis. Variables such as age, gender, underlying disease, presence of cirrhosis, time of HCC diagnosis, alpha-fetoprotein (AFP) levels, time to present thyroid metastasis, survival after HCC, and survival after thyroid metastasis were analyzed.

Case report

A 52-year-old man was diagnosed with Child A cirrhosis due to HCV during routine exams. He underwent treatment with pegylated interferon (PEG-IFN) and ribavirin for 6 months, achieving a sustained virological response. Six years later, he was diagnosed with HCC measuring 3.2 × 2.8 cm in segment II, during routine exams. A left lateral hepatectomy was performed by laparoscopy with the removal of segments II and III. At the time, serum AFP was normal (< 8.0 ng/mL). The biopsy evidenced a well-differentiated HCC, Edmonson-Steiner grade I, without vascular or neural invasion. Four years after surgery, hepatic magnetic resonance imaging (MRI) showed five nodular images suggestive of HCC, located in segments IVa and IVb. AFP was 1.3 ng/mL. The patient was listed on the Brazilian National System of Transplants and was transplanted after a waiting time of 3 months. On macroscopic examination, nine nodules were found, with the largest measuring 1.8 × 1.7 cm in segment IV, characterized as moderately differentiated (grade II) HCC without macroscopic, microscopic, or perineural venous invasion. The pathological staging was considered pT2pNX. Four years after the LT, the patient developed a dry cough and significant dysphagia. A physical examination revealed a hard left thyroid mass with a less pliable consistency. Ultrasound revealed a thyroid nodule measuring 6.5 × 3.8 × 3.9 cm (39.1 cm^3), hypoechoic, vascularized, and TI-RADS 5 (highly suspicious for malignancy). Fine-needle aspiration suggested neoplasia. The patient underwent a total thyroidectomy 3 months later. Histopathological findings were compatible with undifferentiated neoplasia. Immunohistochemistry showed OCH1E5 clones, consistent with metastasis from HCC.

RESULTS

After analyzing six cases with relevant data regarding HCC with thyroid metastasis post-liver transplantation, there is a prevalence of HBV and HCV as etiologies of liver disease (83.3%). Additionally, the time between the diagnosis of HCC and thyroid metastasis was within 3 years. The AFP level (< 8.0 ng/mL in adults, non-pregnant) was elevated in five cases, with a significantly increased value in 50% of cases (> 500 ng/mL). Further details are available in Table 1. Of the seven cases, including the patient in this study, six were reported to have viral hepatitis. Consequently, a chi-square test was performed to evaluate whether viral hepatitis constitutes a risk factor for HCC metastasis. Additionally, AFP levels at the time of diagnosis were compared between HCC patients with and without viral hepatitis. For this analysis, the Liver Transplant Database from Universidade Federal do Ceará (UFC), RedCap,[6] was utilized, comprising data from 729 patients who underwent liver transplantation due to HCC. Data from 523 patients were included in the analysis and processed by Jamovi version 2.3 (R Core Team version 4.1), as it provided sufficient information. No statistically significant difference was found between the two groups. Further details are presented in Tables 2 and 3. AFP levels were elevated in the group of patients with viral hepatitis, as shown in Table 4.

Table 1. Literature review of published cases of HCC with thyroid metastasis.

	Sex	Age[†]	Etiology[‡]	Cirrhotic patient	AFP quantification	Time[§]	Cancer staging	HCC[‖]	TM[¶]
1[7]	Male	54	HBV[††]	ND	162.4	7	pT1N0M0	15	8
2[8]	Male	62	HBV[††]	ND	1.940	0	ND	ND	ND
3[9]	Female	62	HCV[‡‡]	NCP[§§]	12.070	7	pT1NxMx	ND	ND
4[10]	Male	63	HCV[‡‡]	ND	36.7	36	ND	79	43
5[11]	Female	42	HCV[‡‡]	NCP[§§]	7.016	36	pT2N0M0	ND	ND
6[12]	Male	57	ND	ND	1.39	36	ND	48	12

ND = not described.[†]Age of the patient at recurrence with thyroid metastasis; [‡]Etiology of hepatic disease; [§]Time interval between HCC diagnosis and thyroid metastasis in months; [‖]Time elapsed since HCC diagnosis; [¶]Time elapsed since thyroid metastasis diagnosis; [††]Hepatitis B; [‡‡]Hepatitis C; [§§]Non-cirrhotic patient. Source: Elaborated by the authors.

Table 2. Contingency tables.

Viral hepatitis	Metastasis		Total
	0	1	
0	198	10	208
1	286	29	315
Total	484	39	523

Source: Elaborated by the authors.

Table 3. Chi-square tests.

	Value	df	*p*-value
χ^2	3.51	1	0.061
n	523		

Source: Elaborated by the authors.

Table 4. AFP.

	Viral hepatitis	n	Mean	Median	Mode	SD	Percentiles		
							25th	50th	75th
AFP	0	140	445	6.00	2.50	3.854	3.10	6.00	17.5
	1	249	581	13.90	6.60	3.618	5.30	13.90	93.0

Source: Elaborated by the authors.

DISCUSSION

The Hospital Universitário Walter Cantídio (HUWC), affiliated with the UFC, stands as one of the largest LT centers in Brazil, performing an average of 150 transplants annually, with approximately 20% attributed to HCC. While tumor recurrence extended to the 4th year after liver transplantation, occurring within the period of heightened recurrence incidence (first 5 years), the majority of recurrences manifested at the LT site. Thyroid metastases are infrequent, representing 1-3% of all surgeries for malignant thyroid tumors.[13] Although the most prevalent sites for extrahepatic metastases in HCC are the lungs, adrenal glands, bones, and lymph nodes, in thyroid metastases, the renal primary site is the most common (35.82%), followed by the pulmonary (16.14%) and gastrointestinal tracts.[14] The patient in this case had one risk factor for recurrence: multinodular HCC with nine nodules as evidenced by biopsy, exceeding the Milan criteria but falling within the Milan/Brazil criteria (excluding nodules measuring less than 2 cm, adopted in Brazil since 2006).[15] Liver transplantation presents a significant limitation to the systemic treatment of HCC recurrence. It is a formal contraindication to the use of immunotherapy due to the high risk of rejection and potential loss of the hepatic graft.[16]

CONCLUSION

HCC is a potentially aggressive and metastatic neoplasm, with late recurrences documented. This literature review illustrates a rare and late recurrence in the thyroid in a patient previously subjected to hepatectomy and LT. Further analysis of the recurrence of thyroid metastasis due to cellular HCC must be carried out in order to reach conclusive results regarding the risk factors and prognosis.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Viana DDA, Magalhães AEB, Hyppolito EB, Costa PEG. **Conception and design:** Viana DDA, Magalhães AEB, Dias LP, Silva DL, Teixeira LP, Hyppolito EB, Costa PEG. **Data analysis and interpretation:** Viana DDA, Hyppolito EB, Costa PEG. **Article writing:** Viana DDA, Magalhães AEB, Hyppolito EB, Costa PEG. **Critical revision:** Coelho GR, Costa PEG, Dias LP, Garcia JHP, Hyppolito EB, Lima CA, Magalhães AEB, Silva DL, Teixeira LP, Viana DDA. **Final approval:** Hyppolito EB, Costa PEG, Coelho GR, Garcia JHP.

DATA AVAILABILITY STATEMENT

Not applicable.

FUNDING

Not applicable.

ACKNOWLEDGEMENT

PIT/Ebserh/HUWC Technological Initiation Program.

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