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ORIGINAL ARTICLE

Liver Transplantation for Hepatic Epithelioid Hemangioendothelioma - Retrospective Cohort

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ABSTRACT

Introduction: Hepatic epithelioid hemangioendothelioma (HEH) is a rare neoplasm of unknown etiology and guarded prognosis if not diagnosed and treated properly. Resection is the primary treatment, but it is difficult to perform in large and multiple tumors, and liver transplantation (LT) is the most commonly used treatment in these cases. **Objectives:** To describe and analyze the clinical presentation, treatment, and prognosis of patients diagnosed with HEH and submitted to LT. **Methods:** Retrospective analysis of the clinical presentation, treatment, and prognosis of 8 patients undergoing LT due to HEH in two reference hospitals in the Northeast of Brazil. **Results:** A total of 2,413 liver transplants were carried out in two tertiary hospitals, of which only 8 (0.3%) were due to HEH. The median age at transplant was 36.7 (IQR [33.91–38.02]). The most frequent symptom was abdominal pain in the right hypochondrium, present in 6 patients (75.0%). One patient (12.5%) had pretransplant ascites. The calculated MELD was 10 ± 4.44, while the MELD corrected for special situations was 24.25 ± 3.41. One patient progressed to death due to recurrence of the disease with lung metastasis. The remaining patients (87.5%) are being followed up as outpatients with preserved liver function. The overall survival rate for patients at 1 month, 1 year, and 5 years was 100%, 87.5%, and 87.5%, respectively. **Conclusion:** HEH is a rare tumor of which the most common presentation is multinodular. This makes LT the most appropriate treatment with satisfactory long-term results.

Descriptors: Surgical Oncology; Liver Neoplasms; Immunohistochemistry; Survival Analysis.

Transplante Hepático para Hemangioendotelioma Epitelioide Hepático - Cohorte Retrospectiva

RESUMO

Introdução: O hemangioendotelioma epitelioide hepático (HEH) é uma neoplasia rara de etiologia desconhecida e prognóstico reservado, caso não diagnosticado e tratado adequadamente. A ressecção é o principal tratamento, porém é de difícil realização em tumores grandes e múltiplos, sendo o transplante hepático (TH) o tratamento mais usado nesses casos. **Objetivos:** Descrever e analisar a apresentação clínica, o tratamento e o prognóstico de pacientes diagnosticados com HEH e submetidos ao TH. **Métodos:** Análise retrospectiva da apresentação clínica, do tratamento e do prognóstico de 8 pacientes submetidos a TH devido a HEH em dois hospitais de referência no Nordeste do Brasil. **Resultados:** Foram realizados 2.413 transplantes de fígado em dois hospitais terciários, dos quais apenas 8 (0,3%) foram por HEH. A mediana da idade no transplante foi de 36,7 (IQR [33,91–38,02]). O sintoma mais frequentemente presente foi dor abdominal em hipocôndrio direito, presente em 6 pacientes (75,0%). Um paciente (12,5%) apresentava ascite pré-transplante. O MELD calculado foi de 10 ± 4,44, enquanto o MELD corrigido por situação especial foi de 24,25 ± 3,41. Uma paciente evoluiu para óbito por recidiva da doença com metástase pulmonar. Os demais pacientes (87,5%) seguem em acompanhamento ambulatorial com função hepática preservada. A taxa de sobrevida global dos pacientes em 1 mês, 1 ano e 5 anos foi de 100%, 87,5% e 87,5%, respectivamente. **Conclusão:** O HEH é um tumor raro cuja apresentação mais comum é a multinodular. Com isso, o TH se torna o tratamento mais adequado com resultados satisfatórios a longo prazo.

Descritores: Oncologia Cirúrgica; Neoplasias Hepáticas; Imuno-Histoquímica; Análise de Sobrevida.

INTRODUCTION

Epithelioid hemangioendothelioma (EH) is a rare vascular neoplasm of unknown etiology that can affect various organs and tissues. This name was suggested by Weiss and Enzinger in 1982[1] to describe a vascular tumor of endothelial origin with an intermediate clinical presentation between hemangioma and angiosarcoma, that is, a neoplasm with an indolent course, but with a low survival rate: 5% in 5 years.[2,3]

Hepatic epithelioid hemangioendothelioma (HEH) is the presentation of HE in which the liver is the affected organ. It was described in 1984,[4] with an incidence of 0.1 to 1 case per 100,000 inhabitants and predominantly affecting women, with a higher prevalence in the 4th and 5th decades of life.[1] The clinical presentation is heterogeneous, with manifestations ranging from asymptomatic patients in up to 25% of cases or patients with varied symptoms such as abdominal pain, nausea, weight loss, portal hypertension, and liver failure.[2] Diagnosis is based on imaging, biopsy, and biochemical tests, as HEH stains in immunohistochemical assays for vascular markers such as CD34, CD31, and factor VIII.[5] Metastases can occur and are reported in up to 27% of patients, with lungs being the most commonly affected organs.[1]

Hepatic epithelioid hemangioendothelioma is a rare tumor, little known in terms of etiology and pathophysiology, which can be treated with resection in cases of single nodules or unilobar disease, but with the possibility of aggressive recurrence.[6] Liver transplantation (LT) can be indicated in cases of advanced liver involvement without extrahepatic disease, with satisfactory results and overall survival rates at 5 and 10 years of 83% and 74%, respectively.[7]

The data currently available on HEH are mostly from small series and case reports, with few robust cohorts available.[6,8,9] As a result, HEH remains a little-known disease, with no established consensus on the indications for treatment, due to the gap in the literature on the subject.

This study aims to analyze the clinical presentation, treatment, and prognosis of patients diagnosed with HEH undergoing LT.

METHODOLOGY

Patients

Patients who were diagnosed with HEH and transplanted in two tertiary referral hospitals in the Northeast of Brazil by the same team between 2002 and 2023 were analyzed retrospectively. All patients diagnosed with HEH, confirmed by biopsy and immunohistochemical study, and with available clinical, demographic, histological, radiological, and post-transplant follow-up data were included in the study. This study was approved by the institutional ethics committee, with Certificate of Presentation for Ethical Consideration No.: 52980321.3.0000.5045..

Statistical Analysis

The continuous variables were analyzed and presented as medians and interquartile ranges (IQR). Categorical variables were presented as percentages and frequencies. Overall survival and disease-free survival were calculated using the Kaplan–Meier method. Data analysis was carried out using JASP software version 0.18.3.0.

RESULTS

Between 2002 and 2023, 2,413 liver transplants were performed in two tertiary referral hospitals, of which only 9 were due to HEH, and these were included in the analysis. One of the 9 patients who underwent transplantation was excluded from the study after the initial biopsy, suggestive of hemangioendothelioma, changed the diagnosis to carcinoid tumor during the histopathological examination of the liver explant. In our case series, 4 patients diagnosed with HEH were men (50%), the median age at diagnosis was 36.7 (IQR [33.91–38.02]); none of the patients had any underlying pathology associated with HEH. Table 1 describes the characteristics of the study cohort.

All the patients were symptomatic at diagnosis, but with nonspecific signs and symptoms. Six patients (75.0%) presented with abdominal pain, one patient (12.5%) with nausea and vomiting, one patient (12.5%) with pretransplant ascites, and no patient presented with jaundice.

In our series, 8 patients (100%) had multinodular HEH, 3 patients (37.5%) had vascular invasion, 1 patient (12.5%) had lymph node involvement, and no patient had extrahepatic disease at diagnosis (Table 2).

Table 1. Cohort characteristics.

Clinical presentation of the cohort	N
Age (IQR)	36.7 [33.91–38.02]
Male/female, n	4/4
Baseline liver disease, yes/no	0/8
Symptoms at diagnosis	
Abdominal pain	6
Nausea	1
Vomiting	1
Ascites	1
Jaundice	0

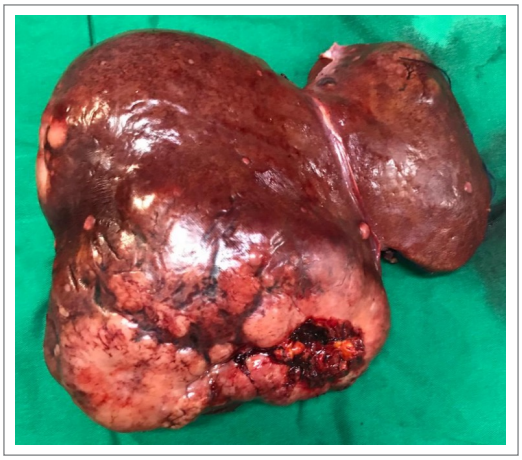
Source: Elaborated by the authors. IQR: interquartile range.

Table 2. Presentation characteristics of HEH.

HEH characteristics	n (%)
Multinodular	8 (100%)
Uninodular	0 (0%)
Vascular invasion	3 (37.5%)
Lymph node involvement	1 (12.5%)
Extrahepatic disease	0 (0%)

Source: Elaborated by the authors.

All patients included in the study underwent a histopathological examination of the liver explant surgical specimen. Macroscopically, the main finding was multiple nodules of firm consistency and whitish color (Fig. 1), measuring between 1.0 and 18.0 cm in size. Five patients (62.5%) had necrosis in the tumor focus, 4 (50.0%) had necrosis in less than 5% of the tumor extension, and 1 (12.5%) had 10% necrosis of the tumor extension.

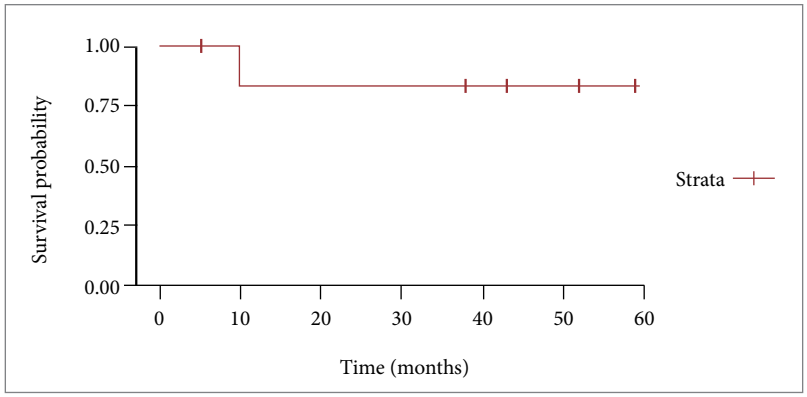


Source: Elaborated by the authors.

Figure 1. Explanted liver with whitish nodules resulting from multifocal HEH.

All the patients had their diagnoses confirmed by immunohistochemistry, in which CD31 and CD34 were present.

The 8 patients in this cohort had multifocal HE and underwent LT. The calculated Model for End-Stage Liver Disease (MELD) of these patients was 10 ± 4.44, while the MELD corrected for special situation was 24.25 ± 3.41. Among the 8 patients, 1 died due to recurrence of the disease with lung metastasis and 1 had a tumor recurrence in the left supraclavicular region, requiring surgery. The overall survival rates for this cohort at 1 month, 1 year, and 5 years were 100%, 87.5%, and 87.5% respectively (Fig. 2). While disease-free survival at 1 month, 1 year, and 5 years were 100%, 75% and 75%, respectively.



Source: Elaborated by the authors.

Figure 2. Survival curve of patients followed up for HEH.

DISCUSSION

Epithelioid hemangioendothelioma is a rare neoplasm that can affect various organs and tissues, with the liver being affected in up to 19% of cases.[4] The incidence of HEH is between 0.1 and 1 case per 100,000 inhabitants and predominantly affects women,[2] but in our sample 50% of patients with HEH are men.

At diagnosis, most patients presented with nonspecific signs and symptoms, the most common findings being pain in the right hypochondrium, hepatomegaly, and weight loss. In addition, up to 25% of patients can be asymptomatic.[10] Less common clinical presentations that are present in more advanced stages are jaundice,[11] portal hypertension, and liver failure.[2] In this cohort, the main clinical finding was abdominal pain in 75% of patients. Ascites was present in 1 patient with advanced HEH and no patient had jaundice. The clinical findings of this study are in line with the literature.[2,10,11]

The diagnosis of HEH is usually incidental, with findings of liver nodules on imaging tests and confirmed by biopsy and immunohistochemical study.[5,12,13] All the patients in this study underwent investigation for nonspecific complaints, with findings of multiple nodules on imaging tests, which were analyzed and diagnosed with HEH through histopathological examination and immunohistochemical study.

The main treatment for HEH is tumor resection, especially for small, single nodules,[14] but HEH commonly presents in a multinodular form.[1,4,12] Therefore, curative resection is often unfeasible and palliative resection should be avoided due to the aggressive behavior of the remaining liver nodules.[2,15] Nonsurgical treatment options have been explored, such as transcatheter arterial chemoembolization, chemotherapy, and radiotherapy[16–18], which can be combined with the surgical modality as a multimodal strategy for the treatment of HEH,[19,20] offering an alternative in cases of unresectable disease or when LT is not available.[19] However, nonsurgical modalities are not widely accepted, as there is little evidence of their effectiveness.[19]

In Brazil, unresectable multinodular HEH without extrahepatic disease is prioritized as a special situation for transplantation. Nevertheless, some services indicate LT for HEH with controlled extrahepatic foci.[14,21] Therefore, LT is the most widely used therapy for the treatment of HEH.[22] In situations where there is no deceased donor available, inter-vivos LT is a possibility.[23–25] Some studies suggest indicating LT for treatment in cases of multinodular HEH with more than 10 nodules, more than 4 affected segments and nodules larger than 10 cm in diameter,[26] and in cases where it is impossible to resect the lesions.[14] In this cohort, 2 patients (25%) had more than 10 nodules, 2 patients (25%) had nodules larger than 10 cm, and 8 patients (100%) had more than 4 segments affected. Thus, LT was the modality of choice for treating these cases.

Liver transplantation shows satisfactory results for the treatment of HEH with 5-year survival of 64%[22] to 71.5%[12] and disease-free survival of 60.2%[12] to 83%.[27] In the present study, 5-year overall survival was 87.5% and disease-free survival was 75%. Two patients had recurrences, 1 in the supraclavicular region, who underwent successful resection, and 1 developed lung metastasis with subsequent death 10 months after transplantation.

As for prognosis, HEH has good prospects with a 5-year survival rate of over 60% when treated with LT.[12,22,27] Tumors larger than 10 cm in diameter are associated with a worse prognosis.[21] In addition, macrovascular infiltration and lymph node involvement are relevant risk factors for HEH recurrence after treatment.[21] In this study, 3 patients had vascular invasion, 2 of whom had tumor recurrence.

CONCLUSION

Hepatic epithelioid hemangioendothelioma is a rare and heterogeneous tumor with a variable evolution, so the therapeutic strategy for these tumors is not standardized. Surgical resection is therefore the first-line treatment for patients with localized tumors, which is an infrequent scenario since they are diagnosed as multinodular. As a result, transplantation has become the most widely used treatment with satisfactory long-term results.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantial scientific and intellectual contributions to the study: Pinheiro PFS, Martins TBP, Matos PELC, Garcia JHP; **Conception and design:** Martins TBP, Pinheiro PFS, Coelho GR, Matos PELC, Costa PEG, Mesquita DFG; **Data analysis and interpretation:** Pinheiro PFS, Martins TBP, Viana DDA, Garcia JHP; **Article writing:** Pinheiro PFS, Martins TBP, Viana DDA; **Critical review:** Pinheiro PFS, Martins TBP, Coelho GR, Mesquita DFG, Costa PEG, Garcia JHP; **Final approval:** Garcia JHP.

DATA AVAILABILITY STATEMENT

Data will be available upon request.

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