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SHORT COMMUNICATION

Hepatocellular carcinoma, an underdiagnosed entity: An autopsy series

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KEYWORDS
Hepatocellular carcinoma;
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Abstract Hepatocellular carcinoma is the most frequent primary malignant tumor of the liver. In Mexico, it is one of the main causes of death. It tends to be detected at late stages of the disease, making its prognosis poor in most cases. It has a wide range of clinical presentation and histologic subtypes, which can also have prognostic implications. We conducted an autopsy study series, in which we identified a total of 34 cases of hepatocellular carcinoma over a 6-year period, accounting for 1.37% of all the postmortem studies. The disease was slightly more frequent in men, with a 1.42:1 ratio, and in the sixth decade of life. The conventional subtype was more frequent, and the main cause of death was hypovolemic shock due to gastrointestinal bleeding. A striking datum was that only 38.2% of the cases were diagnosed before the autopsy report, underlining the need to improve protocols for the early detection of hepatocellular carcinoma.

PALABRAS CLAVE
Carcinoma hepatocelular;
Autopsia;
Cirrosis

Carcinoma hepatocelular, una entidad subdiagnosticada: una serie de autopsias

Resumen El carcinoma hepatocelular es la neoplasia maligna primaria más frecuente del hígado, en México representa una de las principales causas de mortalidad. Suele detectarse en estadios tardíos de la enfermedad, por lo que su pronóstico es malo en la mayoría de los casos. Existe una amplia gama de presentación clínica y subtipos histológicos, mismos que pueden tener implicaciones pronósticas. Realizamos una serie en estudios de autopsia en la que identificamos un total de 34 casos de carcinoma hepatocelular en un periodo de 6 años, representando el 1.37% del total de los estudios postmortem. Fue ligeramente más frecuente en hombres, con una relación de 1.42:1, en la sexta década de vida, con mayor frecuencia presentándose el subtipo convencional, y el principal motivo del fallecimiento siendo el choque

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hipovolémico por sangrado de tubo digestivo. Un dato llamativo fue que solo el 38.2% de casos se diagnosticó antes del estudio de autopsia, que nos plantea la necesidad de mejorar los protocolos para la detección temprana de esta neoplasia.

Introduction and aims

Hepatocellular carcinoma (HCC) is the most frequent primary malignant tumor of the liver and one of the main causes of cancer death worldwide.

Its clinical presentation varies widely, given that even though it is predominant in the adult population, it also presents in youths and can be associated with cirrhotic and non-cirrhotic livers. There is also a wide range of histologic variants, and prognosis is importantly dependent on early detection, among other factors.[1,2]

In Mexico, HCC holds ninth place in the incidence of malignant tumors, and its distribution is similar between the sexes. It is third place in cancer death in women, and fourth place in men. It has been reported as the most prevalent tumor (14 cases/100,000 inhabitants) in women over 65 years of age, surpassing even breast cancer and cervical cancer. The main identified risk factors in the Mexican population include hepatitis C virus infection, alcohol use, and metabolic dysfunction-associated steatotic liver disease,[3,4] formerly known as nonalcoholic fatty liver disease.

Even though the study protocols for liver nodules are well established in patients with cirrhosis, depending on their size and growth rate,[1] not all cases of this cancer are detected. In addition, there are no follow-up protocols for liver nodules in patients without cirrhosis, who can also develop malignant tumors.

Therefore, our aim was to describe the characteristics of HCC in autopsy reports and to determine the percentage of cases that were not identified until the postmortem study was carried out.

Material and methods

We conducted a retrospective, descriptive, observational study, in which we reviewed all the autopsy studies from the *Hospital General de México ''Dr. Eduardo Liceaga''*, performed within the time frame of January 2013 and December 2018. We selected the reports whose final diagnosis was ''hepatocellular carcinoma''. We included all the cases with complete reports and optimal material for their review. Due to the nature of the study, we did not apply elimination criteria, nor did we carry out any sampling method, given that we included all the cases identified with the diagnosis of interest. We utilized the fifth edition of the 2019 World Health Organization Classification of Tumors series.[5] It should be emphasized that the conventional subtype includes 4 morphologic patterns: trabecular, pseudo-glandular, solid, and macrotrabecular. This last pattern included in the conventional subtype must be differentiated from the so-called massive macrotrabecular subtype, which is considered to have worse prognosis and is molecularly defined by P53 mutations and FGF19 amplification. In our study, we only took the histologic subtypes into account, without specifying the morphologic patterns. The results were reported using descriptive statistics.

Results

From January 2013 to December 2018, a total of 2,465 autopsies were performed, identifying 34 cases of hepatocellular carcinoma and accounting for 1.37% of the autopsies carried out.

Patient age ranged from 25 to 82 years, with a mean of 60 years. Twenty cases corresponded to men and 14 to women, with male sex predominating at a 1.42:1 ratio.

The following histopathologic subtypes were identified: the conventional subtype in 13 cases (38.2%), the macrotrabecular subtype in 10 cases (29.4%), undifferentiated carcinoma in 6 cases (17.6%), fibrolamellar carcinoma in 2 cases (5.8%), the combination of HCC and cholangiocarcinoma in 2 cases (5.8%), and clear cell carcinoma in one case (2.9%).

Clinically, 31 cases (91.1%) had a history of cirrhosis of the liver, diagnosed in life through physical examination and imaging studies, and corroborated in the autopsy study, both macroscopically and microscopically. Of the total of HCC cases, only 13 (38.2%) were diagnosed before the autopsy study (Table 1).

In the male group, age ranged from 24 to 77 years, with a mean of 60 years. The histopathologic subtypes were conventional, with 8 cases (40%), undifferentiated carcinoma, with 4 cases (20%), macrotrabecular, with 3 cases (15%), fibrolamellar and combined carcinoma, with 2 cases each (10%), and clear cell carcinoma, with one case (5%). There was metastasis to other organs in the cases of conventional carcinoma, fibrolamellar carcinoma, undifferentiated carcinoma, and combined carcinoma, each subtype with 2 cases (10% for each one). The lung and para-aortic lymph nodes were more frequently affected. Three cases (15%) presented with portal invasion (conventional, combined, and fibrolamellar subtypes, with one case each). Clinically, 18 cases (90%) had a previous diagnosis of cirrhosis of the liver, and the 2 remaining cases (patients 24 and 25 years of age) had fibrolamellar carcinoma. The most frequent cause of death in the male group was hypovolemic shock due to

Table 1 Characteristic of hepatocellular carcinoma in autopsies, by sex.

	Males	Females	Total
Cases	20 (58.8%)	14 (41.1%)	34 (100%)
Histologic subtype			
Conventional	8 (40%)	5 (35.7%)	13 (38.2%)
Macrotrabecular	3 (15%)	7 (50%)	10 (29.4%)
Undifferentiated carcinoma	4 (20%)	2 (14.2%)	6 (17.6%)
Clear cell	1 (5%)	0 (0%)	1 (2.9%)
Fibrolamellar	2 (10%)	0 (0%)	2 (5.8%)
Combined hepatocellular carcinoma and cholangiocarcinoma	2 (10%)	0 (0%)	2 (5.8%)
Cirrhosis	18 (90%)	13 (92.8%)	31 (91.1%)
Cause of death			
Hypovolemic shock	8 (40%)	5 (35.7%)	13 (38.2%)
Fluid-electrolyte imbalance	7 (35%)	8 (57.1%)	15 (44.1%)
Septic shock due to peritonitis	2 (10%)	0 (0%)	2 (5.8%)
Acute myocardial infarction	1 (5%)	0 (0%)	1 (2.9%)
Septic shock due to pneumonia	1 (5%)	0 (0%)	1 (2.9%)
Brain hemorrhage	1 (5%)		1 (2.9%)
Respiratory failure due to lung metastasis	0 (0%)	1 (7.1%)	1 (2.9%)
Premortem diagnosis	6 (30%)	7 (50%)	13 (38.2%)
Large portal branch invasion	3 (15%)	3 (21.4%)	6 (17.6%)
Distant metastasis	8 (40%)	4 (28.5%)	12 (35.2%)

gastrointestinal bleeding in 8 cases (40%), followed by fluid-electrolyte imbalance in 7 cases (35%). Only 6 cases (30%) of HCC were diagnosed in life in the males.

In the female group, the age range was 53–82 years, with a mean of 65 years. According to histopathologic subtype, there were 7 cases (50%) of the macrotrabecular subtype, 5 cases (35.7%) of the conventional subtype, and 2 cases (14.2%) of undifferentiated carcinoma. Metastasis was present in 2 of the macrotrabecular cases, one of the conventional cases, and one of the undifferentiated carcinoma cases. Liver hilum and peripancreatic lymph nodes were more frequently affected and 3 cases had portal invasion. Clinically, 13 cases (92.8%) had a previous diagnosis of cirrhosis of the liver. The main causes of death in the female group were fluid-electrolyte imbalance in 8 cases (57.1%), followed by hypovolemic shock due to gastrointestinal bleeding in 5 cases (35.7%). Only 7 (50%) female patients were diagnosed with HCC before the autopsy study.

Table 1 gives a detailed description of the characteristics for both sexes.

Specifically, of the 13 cases of HCC that were diagnosed in life, mean patient age was 55 years, and female sex predominated over male sex, with 8 cases (61.5%) and 5 cases (38.4%), respectively. The most frequent etiology identified was alcohol use, with 8 cases (61.5%), and undetermined in the other 5 cases. According to the modified Barcelona Clinic Liver Cancer (BCLC) staging system, 8 cases were advanced stage (C) (61.5%), 3 were end-stage (D) (23.0%), and 2 were intermediate stage (B) (15.3%). No case underwent chemoembolization or systemic therapy. The most frequent cause of death in that group was fluid-electrolyte imbalance associated with liver failure, with 7 cases (53.8%), followed by hypovolemic shock, with 4 cases (30.7%), septic shock, with one case (7.6%), and respiratory insufficiency due to lung metastases, with one case (7.6%).

Notably, lung metastases were identified in one case, but the patient died before determining the primary site of the tumor. In 3 cases, multiple liver nodules were identified in patients with data of liver failure or cirrhosis, but clinical suspicion was metastatic disease, and the patients died during the protocol for determining the primary site of the lesion, which was confirmed to be the liver in the postmortem study.

Discussion

The estimated frequency of HCC is 0.9–1.5% in autopsy studies, similar to the 1.37% in our series, albeit frequency has also been reported up to 6.08%.[6–8] In Mexico, there are no previous reports with which to compare frequency.

According to the international literature, HCC is more frequent in men, at a ratio of 3:1, and that ratio has also been reported in Mexico.[9] However, other reports consider there is not a statistically significant difference between sexes,[3] as in our study.

Regarding the histopathologic subtypes, the conventional subtype is the most frequent, the same as in our study. A total of 29.4% of our cases had macrotrabecular carcinoma, which is higher than the 5% reported in the literature. Likewise, undifferentiated carcinoma had a frequency of 17.6%, which is rather high, given that it is considered a rare tumor. However, its prognosis is also poor, compared with other HCC subtypes, and so its elevated mortality rate could explain a greater identification in autopsy cases.[5]

Knowing the histopathologic variants of HCC is not the only important factor to have in mind. We must emphasize that in 3 of the cases of our series, liver nodules were identified in a background of liver injury and the clinical suspicion noted in the case records was metastatic disease, overlooking the possibility of a primary liver tumor, until reported

in the autopsy. Knowing that HCC can have a multinodular and/or diffuse macroscopic aspect may be the key to making the correct diagnosis.

Cirrhosis was identified in 91.1% of our cases, similar to that reported in the literature.[10] Surprisingly, in an autopsy series reviewed, only 19% of the cases were diagnosed with cirrhosis, which increased to 71% after the postmortem study. This underlines the possibility that certain variables associated with HCC can be overlooked clinically,[11] highlighting the importance of autopsy, even today.

In our review of the literature, we found only one series reporting the discovery of HCC until autopsy in 63% of the cases, similar to our 61.7%. These percentages are quite high and suggest the possibility of considering improvements in the diagnostic and follow-up methods of patients with liver lesions.

Lastly, the most frequent causes of death in our series were hypovolemic shock due to gastrointestinal bleeding and fluid-electrolyte imbalance, underlining the fact that those mechanisms appear to be more closely associated with cirrhosis than with cancer. Nevertheless, the destructive and debilitating factor of HCC obviously greatly contributes to patient death.

In conclusion, HCC is a complex entity with a wide gamut of histopathologic subtypes and clinical characteristics, making it a difficult cancer to detect, given that more than 60% are not diagnosed in life. We must ask ourselves how we can improve the diagnostic and follow-up protocols for liver tumors in our environment and be currently reminded of the importance of autopsy studies, to improve the quality of medical care.

Ethical considerations

This study was conducted following all bioethical norms. It was reviewed and approved by the retrospective study ethics committee of the *Hospital General de México ''Dr. Eduardo Liceaga''*, with registry number DECS/JPO-CT-572-2020.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

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