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HEPATIC VIRUSES AND THEIR ROLE IN THE DEVELOPMENT OF HEPATOCELLULAR CARCINOMA: A CLINICAL STUDY OF 190 PATIENTS

Alina Elisabeta Lehaci[1], D. V. Scripcariu[1,2*], Ruxandra Teodora Stan[1], A. Vâță[1,3], I. M. Onofrei[1,3], C. M. Luca[1,3], A. M. Dumitrescu[1,4], Anca Sava[1,4]

1. Grigore T. Popa University of Medicine and Pharmacy, Iasi, Romania,
2. Regional Institute of Oncology, Iasi
3. Sf. Parascheva Clinical Hospital of Infectious Diseases, Iași
4. Prof. Dr. Nicolae Oblu Emergency Clinical Hospital, Iasi, Romania

[*]Corresponding author. E-mail: dragos-viorel.scripcariu@umfiasi.ro

CLINICAL CHARACTERISTICS, COMORBIDITIES, AND RISK FACTORS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA: A COMPARATIVE STUDY OF 190 PATIENTS (Abstract): Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related mortality worldwide, with chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections representing its major etiological factors. **Aim:** To evaluate the etiological, demographic, and clinical characteristics of patients with HCC and to compare patients with HCC alone and HCC associated with liver cirrhosis. **Materials and methods:** This retrospective study included 190 patients diagnosed with HCC over a 10-year period. Demographic data, age at disease onset, etiology, comorbidities, lifestyle-related risk factors, and clinical outcomes were analyzed. Comparisons between groups were performed using Student's *t*-test and Pearson's χ^2 test. **Results:** The mean age at disease onset was 56.2 ± 13.7 years, with no significant differences according to sex (p = 0.820) or disease group (p = 0.839). HCV infection was the most frequent etiology (33.2%), followed by toxic hepatitis (26.8%) and chronic HBV infection (15.3%). Hypertension (22.6%), obesity (35.3%), smoking (44.2%), and alcohol consumption (30.0%) were common. Patients with HCC associated with cirrhosis reported significantly higher alcohol consumption than those with HCC alone (41.3% *vs.* 21.8%; p = 0.004), while smoking reached the threshold of statistical significance (52.5% *vs.* 38.2%; p = 0.050). During the 10-year follow-up, 25 deaths (13.2%) were recorded. **Conclusions:** HCV remains the predominant etiological factor for HCC in the studied population. Alcohol consumption was significantly more frequent among patients with HCC associated with cirrhosis, emphasizing the importance of modifiable risk factors in HCC prevention and management. **Keywords:** HCC, HBV, HCV, CH, ALCOHOL CONSUMPTION, SMOKING.

INTRODUCTION

Viral hepatitis refers to a group of infectious diseases of the liver caused by hepatitis viruses A, B (HBV), C (HCV), D, and E, which differ in terms of transmission mechanisms, clinical manifestations, disease progression, and the risk of chronicity. Unlike hepatitis B and C, hepatitis A, E, and G are not associated with the development of HCC, as they do not lead to chronic infections, which are a major risk factor for liver cancer (1).

In immunocompromised patients, hepatitis E virus infection can progress to chronic hepatitis, with a risk of liver fibrosis and cirrhosis.

HCC is the most common primary malignant tumor of the liver, ranking sixth in incidence and third in cancer mortality worldwide (2).

MATERIALS AND METHODS

We conducted a retrospective observational study that included 190 patients diagnosed with chronic hepatitis caused by hepatitis B, D, and C viruses over a 10-year period, drawn from a patient population in the northeastern region of Moldova at the "Sfanta Parascheva" Clinical Hospital for Infectious Diseases in Iasi (in accordance with the opinion of the Scientific Research Ethics Committee No. 548/03.03.2025), which included 624 individuals.

An analysis of patient outcomes over the 10-year follow-up period revealed 25 deaths (13.2% of the study cohort). Most deaths occurred among men, who accounted for 80.0% of all cases (20 patients), compared with 20.0% among women (5 patients).

Statistical Analysis. The statistical analysis was performed using SPSS 31.0. Qualitative variables were reported as absolute frequencies and percentages, while quantitative variables were reported using standard descriptive statistics (mean, standard deviation, minimum and maximum values, median, and interquartile range). The Pearson chi-square test was used to compare qualitative variables across samples, and the *Student's t*-test was used to compare quantitative variables, after first verifying that their values followed a normal distribution (using the Shapiro-Wilk test). p-values < 0.05 were considered statistically significant, and p-values < 0.01 were considered highly statistically significant

RESULTS

Following the analysis of the data, regarding viral hepatitis and the development of HHC were identified the distribution of patients by study year presented in first figure.

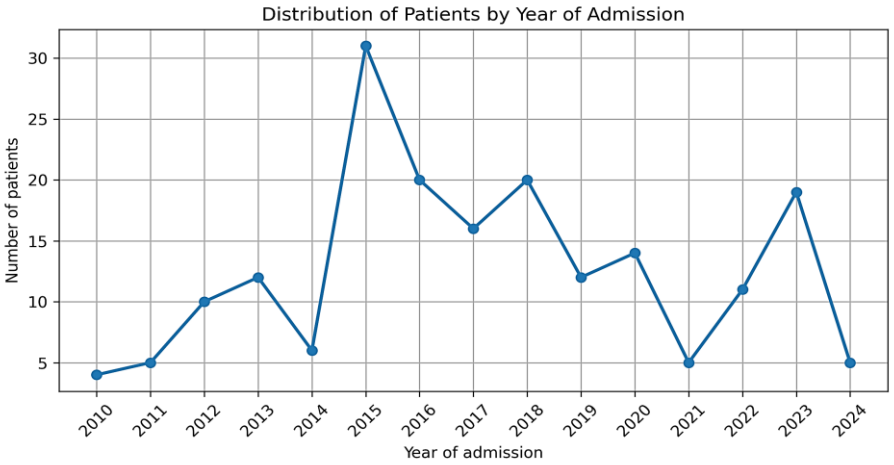

Fig. 1. Line chart showing the annual distribution of patients included in the study (2010-2024).

In the sample of patients with chronic hepatitis B and C who developed hepatocellular carcinoma, there were 71 women (37.4%) and 119 men (62.6%), resulting in a male-to-female ratio of approximately 1.68: 1.

Table I shows the participants by age group and sex; the largest group consists of individuals over 60 years of age, totaling 77 subjects (49 men and 28 women). The 51-60 age group included 43 participants (27 men and 16 women), and the 41-50 age group comprised 44 participants (27 men and 17 women). As for the younger age groups, the 31-40 age group included 20 participants (12 men and 8 women), and the 20-30 age group included 6 participants (4 men and 2 women). There was a gradual increase in the number of participants with advancing age, with a significant concentration in the age groups over 50 years. In contrast, no significant differences were observed between the sexes regarding the distribution of patients across age groups.

TABLE I.

Distribution of patients according to age group and sex

Age group	Male n (%)	Female n (%)	Total n (%)	Pearson Chi-square test
20-30 years	4 (3.4)	2 (2.8)	6 (3.2)	
31-40 years	12 (10.1)	8 (11.3)	20 (10.5)	
41-50 years	27 (22.7)	17 (23.9)	44 (23.2)	p = 0.997
51-60 years	27 (22.7)	16 (22.5)	43 (22.6)	
>60 years	49 (41.2)	28 (39.4)	77 (40.5)	
Total	119 (100.0)	71 (100.0)	190 (100.0)	

The results show a concentration of cases among patients over the age of 50, with no statistically significant differences between the sexes in terms of distribution by age group (Pearson's χ^2 test, p = 0.997).

The mean age of patients who developed liver cirrhosis is 60 years, for hepatocellular carcinoma it is 63 years, and for those with metastases it is 67 years (tab. II).

TABLE II.

Descriptive statistics of age variables

Variable	N	Mean	Std. deviation	Min	Max	Median	IQR
Age at onset	190	56.20	13.685	22	85	56.00	43.00÷ 69.00
Age at MTS	35	67.46	10.920	29	93	67.00	60.50÷ 70.00
Age at CH	100	59.90	11.171	25	87	60.00	55.00÷ 70.50
Age at HCC	190	62.97	11.958	25	93	64.00	59.50÷ 70.50

The means and medians are very close for all the variables analyzed, suggesting relatively symmetrical data distributions and the absence of outliers that would significantly influence the mean. The mean age at onset was 56.20 ± 13.69 years (median = 56 years), with a wide range of variation (22-85 years), indicating considerable heterogeneity in the study population.

Age at the time of MTS recorded the highest mean (67.46 ± 10.92 years), but this estimate should be interpreted with caution due to the small number of cases (N = 35). Variability is moderate, and the interquartile range (60.5-70 years) shows that the central half of the patients is concentrated around the seventh decade of life.

For the CH variable, the mean was 59.90 ± 11.17 years, and the median was 60 years, confirming a balanced distribution. The range (25-87 years) and standard deviation indicate moderate dispersion of the data.

The largest category, represented by HCC (N = 190), had a mean age of 62.97 ± 11.96 years, with a median of 64 years and an interquartile range of 59.5-70.5 years. The fact that the median is slightly higher than the mean may suggest a slight skew toward lower values, but the difference is small and does not indicate a significant deviation from symmetry.

Comparing the standard deviations, it can be seen that they are relatively close (approximately 11-14 years), indicating a similar degree of variability among the groups. The greatest variation was observed for age at onset (SD = 13.69 years), suggesting that the timing of disease onset is more heterogeneous than the other variables analyzed.

The distribution of age at disease onset by sex shows the mean age at onset was 56.03 ± 13.19 years for men and 56.49 ± 14.56 years for women. The median was identical in both groups (56 years), and the interquartile ranges were comparable (47-65 years in men and 46-67 years in women), suggesting a similar distribution of values. The Student's t-test did not reveal any statistically significant differences between the sexes regarding age at disease onset (p = 0.820) (tab. III).

TABLE III.

Age at disease onset according to sex

Age at disease onset	N	Mean	Standard deviation	Min	Max	Median	IQR	Student's t-test
Male	119	56.03	13.194	24	84	56.00	47.00-65.00	p = 0.820
Female	71	56.49	14.562	22	85	56.00	46.00-67.00	

Regarding the distribution of diagnoses at the time of admission in the study sample, the most common diagnosis was chronic hepatitis C, identified in 63 patients (33.2%), followed by toxic hepatitis (drug-induced or alcohol-induced), present in 51 patients (26.8%), and chronic hepatitis B, found in 29 patients (15.3%). Other diagnoses included chronic hepatitis B+D (10 patients; 5.3%), HIV/AIDS (6 patients; 3.2%), chronic hepatitis B+C+D (2 patients; 1.1%), chronic hepatitis B+C (1 patient; 0.5%), and other conditions (sepsis, urinary tract infection, endocarditis, liver abscess, and SARS-CoV-2 infection), totaling 17 patients (8.9%) (tab. IV).

A comparative analysis by sex did not reveal any statistically significant differences in the distribution of diagnoses at admission ($p > 0.05$). However, descriptively, chronic hepatitis B was present in 21 men (17.6%) and 8 women (11.3%), while chronic hepatitis C was identified in 30 men (25.2%) and 33 women (46.5%).

These differences reflect the distribution observed in the sample; however, in the absence of statistical significance, they cannot be extrapolated to the general population.

TABLE IV.
Distribution of participants by admission diagnosis and sex

Admission diagnosis	Male N	%	Female N	%	Total N	%	Pearson's χ^2 test
Toxic hepatitis	37	31.1	14	19.7	51	26.8	**p = 0.157**
Chronic hepatitis B	21	17.6	8	11.3	29	15.3	
Chronic hepatitis C	30	25.2	33	46.5	63	33.2	
Chronic hepatitis B + D	7	5.9	3	4.2	10	5.3	
Chronic hepatitis B + C	1	0.8	0	0.0	1	0.5	
Chronic hepatitis B + C + D	2	1.7	0	0.0	2	1.1	
Liver cirrhosis	7	5.9	4	5.6	11	5.8	
AIDS	3	2.5	3	4.2	6	3.2	
Other	11	9.2	6	8.5	17	8.9	
Total	**119**	**100.0**	**71**	**100.0**	**190**	**100.0**	

It is important to note that all of these patients developed hepatocellular carcinoma at some point in their lives.

The distribution of the comorbidities and associated risk factors in the cohort of 190 patients with HHC shows that essential hypertension (EH) was the most common, identified in 43 patients (22.6%), followed by type 2 diabetes mellitus, present in 27 patients (14.2%). Other cardiovascular conditions were recorded in 11 patients (5.8%), atrial fibrillation and kidney disease in 10 patients each (5.3%), and respiratory disease in 5 patients (2.6%). Grade I/II obesity was present in 67 patients (35.3%) (tab. V).

Regarding lifestyle-related risk factors, 84 patients (44.2%) were smokers. Alcohol consumption was reported by 57 patients (30.0%), of whom 49 reported chronic ethanol consumption, 6 consumed both wine and beer, and 2 reported a daily consumption of approximately three glasses of wine. Another 54 patients reported occasional alcohol consumption, limited to certain social events; these patients were not included in the "alcohol consumers" category used in the study analysis (tab. VI).

Associated neoplasms were identified in 32 patients (16.8%), including breast cancer, prostate adenoma, peritoneal carcinomatosis, and resected colon cancer. Metastases (MTS) were present in 35 patients (18.4%), with sites in the lungs, liver, and bones (tab. V)

TABLE V.
Associated comorbidities and risk factors

Variable	Category	N	%
Associated comorbidities	Essential arterial hypertension	43	22.6
	Atrial fibrillation	10	5.3
	Other cardiovascular diseases	11	5.8
	Type 2 diabetes mellitus	27	14.2
	Respiratory disease	5	2.6
	Renal disease	10	5.3
Obesity		67	35.3
Smoking		84	44.2
Alcohol consumption		57	30.0
Neoplasms		32	16.8
Metastases		35	18.4
Total		**190**	**100.0**

For the comparative analysis, patients were divided into two groups: patients diagnosed with hepatocellular carcinoma and patients with hepatocellular carcinoma associated with liver cirrhosis (tab. VI). Of the total 190 patients included in the study, 110 (57.9%) were diagnosed with hepatocellular carcinoma, and 80 (42.1%) with hepatocellular carcinoma associated with liver cirrhosis.

A comparative analysis of age at diagnosis revealed no statistically significant differences between the two groups (*Student's t*-test, p = 0.839). The mean age at diagnosis was 56.37 ± 14.56 years in the hepatocellular carcinoma group and 55.96 ± 12.47 years in the hepatocellular carcinoma group associated with liver cirrhosis. Furthermore, the median values were comparable between the groups (58.5 *vs.* 55.0 years), suggesting a similar distribution of age at onset in the two patient categories (tab. VI).

TABLE VI.
Descriptive statistics of age at disease onset by disease group

Age at disease onset	N	Mean	Standard deviation	Min	Max	Median	IQR	Student's t-test
Hepatocellular carcinoma	110	56.37	14.558	24	85	58.50	46.00÷65.25	**p = 0.839**
Hepatocellular carcinoma + liver cirrhosis	80	55.96	12.471	22	85	55.00	47.00÷66.00	

Table VII presents a comparative analysis of the clinical and demographic characteristics of patients with hepatocellular carcinoma and those with hepatocellular carcinoma associated with liver cirrhosis. No statistically significant differences were

identified between the two groups in terms of gender distribution (Pearson's χ^2 test, p = 0.212). Men constituted the majority of patients in both groups, accounting for 66.4% of the hepatocellular carcinoma group and 57.5% of the hepatocellular carcinoma group associated with liver cirrhosis.

TABLE VII.

Comparison of demographic, clinical characteristics and risk factors between patients with hepatocellular carcinoma and hepatocellular carcinoma associated with liver cirrhosis

Variable	Category	HCC N	%	HCC + Cirrhosis N	%	Pearson's χ^2 test
Sex	Male	73	66.4	46	57.5	p = 0.212
	Female	37	33.6	34	42.5	
Age at onset	20-30 years	5	4.5	1	1.3	p = 0.321
	31-40 years	12	10.9	8	10.0	
	41-50 years	23	20.9	21	26.3	
	51-60 years	21	19.1	22	27.5	
	>60 years	49	44.5	28	35.0	
Obesity	Present	36	32.7	31	38.8	p = 0.391
	Absent	74	67.3	49	61.3	
Smoking	Present	42	38.2	42	52.5	p = 0.050
	Absent	68	61.8	38	47.5	
Alcohol consumption	Present	24	21.8	33	41.3	p = 0.004
	Absent	86	78.2	47	58.8	
Neoplasms	Present	21	19.1	11	13.8	p = 0.331
	Absent	89	80.9	69	86.3	
Metastases	Present	22	20.0	13	16.3	p = 0.510
	Absent	88	80.0	67	83.8	
Arterial hypertension	Present	26	23.6	17	21.3	p = 0.698
	Absent	84	76.4	63	78.8	
Atrial fibrillation	Present	7	6.4	3	3.8	p = 0.523
	Absent	103	93.6	77	96.3	
Other cardiovascular diseases	Present	6	5.5	5	6.3	p = 1.000
	Absent	104	94.5	75	93.8	
Type 2 diabetes mellitus	Present	16	14.5	11	13.8	p = 0.877
	Absent	94	85.5	69	86.3	
Respiratory disease	Present	4	3.6	1	1.3	p = 0.400
	Absent	106	96.4	79	98.8	
Renal disease	Present	7	6.4	3	3.8	p = 0.523
	Absent	103	93.6	77	96.3	
Total		110	100.0	80	100.0	

The distribution of patients by age group at diagnosis was comparable between the two cohorts, with no statistically significant differences (Pearson's χ^2 test, p = 0.321). In both groups, the largest proportion of patients fell into the age category of over 60 years (44.5% and 35.0%, respectively).

The prevalence of obesity was comparable between the two groups (32.7% *vs.* 38.8%), with no statistically significant differences (Pearson's χ^2 test, p = 0.391). In contrast, differences were observed regarding lifestyle-related risk factors. The proportion of smokers was higher in the group of patients with hepatocellular carcinoma associated with liver cirrhosis than in the group of patients with hepatocellular carcinoma (52.5% *vs.* 38.2%), with the difference reaching the threshold for statistical significance (Pearson's χ^2 test, p = 0.050).

No statistically significant differences were observed between the two groups regarding the prevalence of associated neoplasms (19.1% *vs.* 13.8%; p = 0.331), the presence of metastases (20.0% *vs.*16.3%; p = 0.510), essential hypertension (23.6% *vs.* 21.3%; p = 0.698), atrial fibrillation (6.4% *vs.* 3.8%; p = 0.523), other cardiovascular conditions (5.5% *vs.* 6.3%; p = 1.000), type 2 diabetes (14.5% *vs.* 13.8%; p = 0.877), respiratory impairment (3.6% *vs.* 1.3%; p = 0.400), or renal impairment (6.4% *vs.* 3.8%; p = 0.523).

Overall, the two groups had similar demographic and clinical characteristics, with no significant differences in terms of sex, age at diagnosis, obesity, comorbidities, and the presence of metastases.

In contrast, patients with hepatocellular carcinoma associated with liver cirrhosis had a significantly higher prevalence of alcohol consumption (p = 0.004), and the proportion of smokers was also higher in this group, with the difference reaching the threshold for statistical significance (p = 0.05).

The study also included a histopathological and immunohistochemical analysis of a case of hepatocellular carcinoma with bone metastases, to highlight the morphological characteristics and immunophenotypic profile of the tumor.

Histopathological aspects of hepatocellular carcinoma

In the study cohort, metastases were present in 35 patients (18.4%), with the most common sites being the lungs, liver, and bones. Although bone involvement is less common in HCC, it can represent the initial manifestation of the disease. To illustrate this rare clinical presentation in medical practice, we present the case of a patient in whom bone metastases were the key finding leading to the diagnosis of hepatocellular carcinoma secondary to chronic HBV infection.

Hepatocellular carcinoma most commonly metastasizes to the lungs, abdominal lymph nodes, adrenal glands, spine, and mandible (3).

Bone metastases originating from liver cancer are rare. We present a case of bone metastases that revealed hepatocellular carcinoma (HCC) caused by hepatitis B virus (HBV) infection (4). The case of a 49-year-old man, D.F., who presented with cervico brachialgia and motor deficit in the upper extremities that had persisted for 3 weeks, in the context of a general malaise characterized by asthenia, anorexia, and weight loss, with no history of trauma or abdominal pain. The clinical examination revealed cervical syndrome and hepatomegaly. Abdominal ultrasound showed a multinodular liver, and computed tomography of the spine revealed osteolytic lesions at C7**.** Laboratory tests indicated a syndrome of hepatic cytolysis, hepatic cholestasis, and hepatocellular failure, and serol-

ogy for hepatitis B was positive. The imaging and histopathological diagnosis was established as HCC of viral B etiology, with bone metastasis (5).

Bone metastases originating from hepatocellular carcinoma that developed on lesions of liver cirrhosis caused by hepatitis B virus infection were morphologically of various subtypes, the most common being the trabecular and pseudo glandular subtypes.

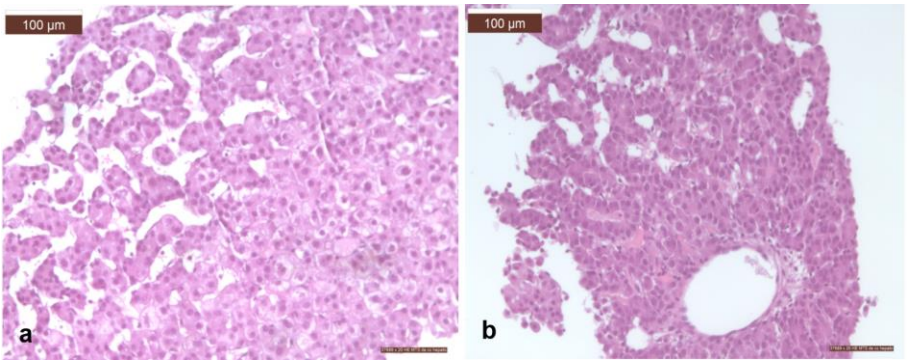

Fig. 2. Microscopic features of an osseous metastasis of a well differentiated hepatocellular carcinoma with trabecular pattern: polygonal cells resembling mature hepatocytes, with mild nuclear atypia, including high Nuclear: Cytoplasmic ratio, irregular nuclear membrane, binucleation and prominent nuclei; cytoplasm varies from clear to eosinophilic, depending on the fat and glycogen content. (a) HE x200; (b). HE x200.

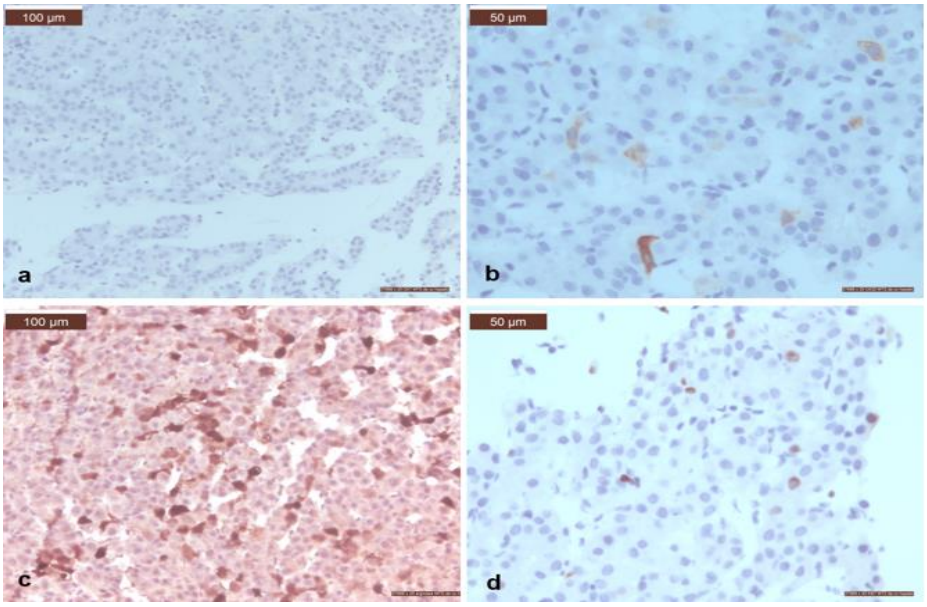

Fig. 3. Same case with immunohistochemical stainings. (a) tumor cells expressed immunonegativity for CK7, (CK7, x200); (b) immunopositivity for CK20 in rare tumor cells (CK20, x400); (c) focal immunopositivity for Arginase of tumor cells (Arginase, x200); (d) low Ki67 Labeling Index (7%), (Ki67, x400).

Bone metastases of well-differentiated hepatocellular carcinoma of the trabecular subtype are shown in using HE (hematoxylin-eosin) and immunohistochemical staining, respectively.

The histological appearance reveals tumor proliferation of epithelial cells arranged in a trabecular pattern, suggestive of hepatocellular origin, supported by the similarity to hepatic architecture and cellular morphology, as well as by the presence of binucleated cells. (figs. 2a 2b, 3a, 3b, 3c, 3d)

Immunohistochemical staining demonstrates immunonegativity for CK7 and focal immunopositivity for CK20 and Arginase. The Ki67 proliferation index has low values (below 7%).

Figure 4 shows tumorous proliferation of epithelial cells arranged in a pseudo glandular pattern and characterized by acini (gland-like spaces) lined with tumor cells that are Arginase+ and also exhibit a low Ki67 labeling index (≤7%).

Silver staining revealed a dense reticulin network delineating the acini.

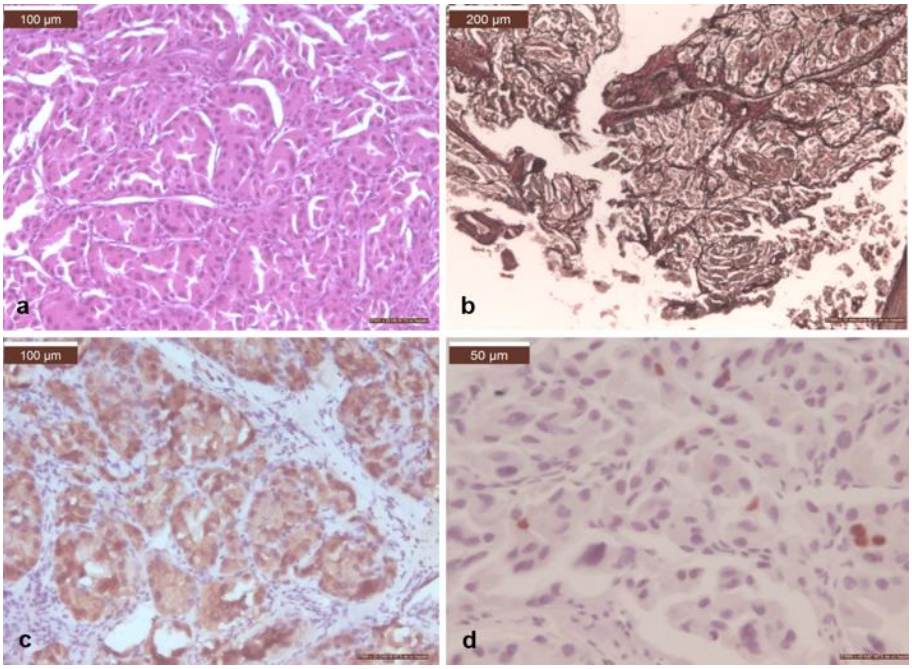

Fig. 4. Microscopic features of an osseous metastasis of a well differentiated hepatocellular carcinoma with pseudoglandular pattern. (a) tumor cells are arranged in an acinar (pseudoglandular) morphology and present similarities with hepatocytes (HE, x200); (b) pseudoglandular structures are delimited by a reticulin network (silver impregnation, x100); (c) tumor cells expressed diffuse cytoplasmatic immunopositivity for CK8/18 (x200); (d) tumor cells expressed low Ki67 Labeling Index (7%) (Ki67, x400).

DISCUSSION

A review of the literature has shown that most cases of HCC with spinal cord metastases involve either the thoracic or

lumbar regions and originate from the right hepatic lobe or both lobes. Although chemotherapy has shown no benefit, surgical management has been shown to reduce morbidity and mortality in some patients (6).

Spinal cord metastasis is a very unusual and rare presentation of HCC. The incidence of bone metastases ranges from 1% to 20%. Due to improvements in diagnosis and therapeutic modalities in recent years, more cases of extrahepatic metastases, particularly bone metastases, have been detected (7, 8).

Although bone metastases are increasingly reported in the literature, bone symptoms as a presenting feature are rare, as our patient presented only with osteoarticular symptoms, without digestive manifestations. The prognosis in HCC with bone metastases is poor, with a median survival of 6.2 months. As with all extrahepatic metastases of HCC, the only therapeutic option remains palliative care (5).

Recent studies in the scientific literature indicate that the main risk factors for hepatocellular carcinoma continue to be chronic infections with hepatitis B and C viruses, liver cirrhosis, excessive alcohol consumption, and metabolic syndrome.

Recent research indicates that people who consume large amounts of alcohol have up to a 5-fold higher risk of developing HCC, while active smokers have more than a 2-fold higher risk (10). In recent decades, there has been a significant increase in the role of non-alcoholic steatohepatitis, obesity, and diabetes mellitus in the pathogenesis of HCC (11).

The results highlight that hepatitis C virus infection is the primary cause associated with the development of hepatocellular carcinoma in the studied cohort, followed by chronic toxic hepatitis and hepatitis B virus infection.

Hepatitis C was identified as the most common cause of hepatocellular carcinoma in the analyzed group (44% of cases), followed by hepatitis B and viral co-infections. In recent years, a gradual shift in the etiological spectrum of hepatocellular carcinoma has been observed, influenced by the implementation of HBV vaccination and direct-acting antiviral therapies for HCV.

Recent epidemiological studies indicate a decline in the proportion of HCC of viral etiology in countries with widespread access to antiviral treatments, accompanied by an increase in the prevalence of steatosis liver disease associated with metabolic dysfunction and alcoholic liver disease.

Non-alcoholic fatty liver disease is increasingly recognized as an emerging cause of hepatocellular carcinoma, closely linked to the rising prevalence of obesity, diabetes mellitus, and metabolic syndrome. In certain cohorts, the contribution of this condition is becoming comparable to that of viral infections. Furthermore, chronic alcohol consumption remains a significant etiological factor.

CONCLUSIONS

The study results confirm that chronic hepatitis C virus infection is the primary etiological factor for hepatocellular carcinoma in the analyzed cohort. The significantly higher prevalence of alcohol and tobacco use among patients with hepatocellular carcinoma associated with liver cirrhosis highlights the contribution of risk factors to the clinical profile of these patients. At the same time, histopathological

analysis demonstrated the importance of morphological and immunohistochemical examination in confirming the diagnosis, including in cases with rare metastases.

These results support the need to strengthen strategies for the prevention of viral hepatitis, the control of risk factors, and the active surveillance of high-risk patients, with a view to early diagnosis and the optimization of hepatocellular carcinoma management. It is important to note that not all patients with chronic viral infection develop HCC.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no specific funding regarding this scientific research.

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