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Clinical and pathological characterization of hepatic lymphomas: a retrospective single-center study

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ABSTRACT – Background – The incidence of hepatic lymphoma has been increasing recently and diagnosis can be challenging as clinical presentation and radiological findings are usually variable and non-specific. **Objective** – The aims of this study were to describe their main clinical, pathological and imaging characteristics and identify poor prognostic factors. **Methods** – A retrospective study that included all patients with histological diagnosis of liver lymphoma over a 10-year period at our center was performed. **Results** – A total of 36 patients were identified, with mean age of 56.6 years and male predominance (58%). There were three patients with primary liver lymphoma (8.3%) and 33 with secondary liver lymphoma (91.7%). The most common histological type was diffuse large B-cell lymphoma (33.3%). The most common clinical manifestations included fever, lymphadenopathy, weight loss, night sweats and abdominal discomfort; three patients (11.1%) were asymptomatic. Computed tomography scan revealed heterogenous radiological patterns including a single nodule (26.5%), multiple nodules (41.2%) or diffuse infiltration (32.4%). The mortality rate during follow-up was 55.6%. Higher levels of C-reactive protein (P=0.031) and absence of treatment response (P<0.001) were significantly associated with higher mortality. **Conclusion** – Hepatic lymphoma is a rare disease that may involve liver as part of a systemic disease or, less commonly, be confined to this organ. Clinical presentation and radiological findings are often variable and non-specific. It is associated with high mortality and poor prognostic factors include higher levels of C-reactive protein and absence of response to treatment.

Keywords – Liver lymphoma; hepatic lymphoma; liver biopsy; liver nodule.

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INTRODUCTION

The incidence of hepatic lymphomas, both primary and secondary, has been steadily increasing over the last several decades[1,2]. Most hepatic lymphomas are secondary as a result of systemic spreading of the lymphoproliferative disease. Primary liver lymphomas are uncommon and are confined to the liver at an early stage without infiltration of other locations, corresponding to 0.4% of extranodal lymphomas and 0.016% of all non-Hodgkin's lymphomas[3]. Intrahepatic solitary/multiple nodules or diffuse infiltration are the most common radiological findings[4]. These features may resemble other intra-hepatic neoplasms including metastatic cancer[5], hepatocellular carcinoma[6] or cholangiocarcinoma[7].

Since liver lymphoma requires chemotherapy instead of surgical excision, an accurate histopathological diagnosis is essential. Liver biopsy remains the most valuable tool for its diagnosis. Several methods, including surgical biopsy, needle core biopsy and fine needle aspiration are available. Surgical biopsy is only used if patients perform an abdominal procedure for other reason. Ultrasound-guided fine needle aspiration has limitations as cytological material alone can not be used for complete histological assessment. Ultrasound-guided percutaneous needle core biopsy is a safe and highly effective method for diagnosis of hepatic mass-like lesions including lymphoma[8].

According to the location of the neoplastic lymphocytes there are three main distinct infiltration patterns: in portal infiltration pattern, these cells are confined to the portal tracts; in nodular infiltration pattern, they are present in hepatic lobules and form nodules; in sinusoidal infiltration pattern, they are dispersed in the sinusoids with preserved lobular architecture[9].

In this retrospective study, we analyzed all cases of liver lymphoma diagnosed in our center over a period of 10 years. The aims of this study were to describe the main clinical, radiological and pathological characteristics of liver lymphoma and identify prognostic factors associated with adverse outcomes.

METHODS

A retrospective study of all patients diagnosed with hepatic lymphoma (both primary and secondary) between January 2010 and December 2019 at *Centro Hospitalar Universitário de São João* (Porto, Portugal) was performed. Patients were selected from a computerized database with every histopathological examinations performed in the Pathology Department, where lymphoma-related terms were searched among all histopathological examinations of liver samples. All patients with confirmed histological diagnosis of lymphoma in a liver sample (biopsy or surgical specimen) were included. Subsequently, demographic data, clinical and pathological features, radiological findings, histological characteristics, therapeutic regimens and outcomes were retrieved from the hospital electronic medical records for each case.

Laboratory and imaging data were based in the nearest blood analysis and computerized tomography (CT) scan from the diagnosis of hepatic involvement by lymphoma, respectively, preferentially before starting any chemotherapy regimen. The biopsies were performed routinely by the radiologists under ultrasound guidance using an 18G Tru-Cut needle or during surgery using wedge resection technique. All routine hematoxylin and eosin stains and immunohistochemical stained slides and other ancillary testing results were reviewed by two pathologists. Different types of lymphoma were classified according to the World Health Organization (WHO) classification of lymphoid neoplasms[10].

Statistical analysis was performed using the SPSS 27.0 software package (IBM Corp., Armonk, NY, USA). For categorical variables, data were expressed as frequencies. For continuous variables, data were expressed as means and standard deviation for variables with normal distribution or median and interquartile range for variables with skewed distribution. The student's *t*-test was used for comparing continuous variables between study groups, with a $P<0.05$ for statistical significance. Categorical variables were compared using Chi-square or Fisher's exact test.

RESULTS

Patient characteristics

A total of 36 patients with liver lymphoma, 21 (58%) males and 15 (42%) females, were identified. Their main demographic, clinical, pathological and imaging characteristics are summarized in TABLE 1. Only 3 (8.3%) patients were diagnosed with primary liver lymphoma; most cases (91.7%) corresponded to secondary lymphoma with involvement of other organs, most commonly lymph nodes (69.5%), bone marrow (52.8%) and spleen (41.6%). Hepatic involvement was detected at the initial presentation of lymphoma in 27/36 (75%) patients (including the 3/3 patients with primary hepatic lymphoma and 24/33 patients with secondary hepatic lymphoma), whereas in 9/36 (25%) it was preceded by the diagnosis of systemic lymphoma by a mean (± standard deviation) of 19.56 (±5.42) months (range 1–47). Therefore, the mean age of the initial diagnosis of lymphoma was 52.11 (±2.19) years, whereas hepatic involvement by lymphoma was detected at a mean age of 56.6 (±13.08) years. Liver biopsy was ultrasound-guided in 29/36 (80.6%) cases and surgical in 7/36 (19.4%) cases.

The most common clinical manifestations included fever (44.4%), lymphadenopathy (44.4%), weight loss (41.7%), fatigue (41.7%), night sweats (33.3%), abdominal discomfort (25%), back pain (13.9%), anorexia (8.3%) or jaundice (6.1%). Three patients (8.3%) were asymptomatic at the time of diagnosis, whereas in five patients (13.9%) the disease had an acute presentation as sepsis (source of infection including pneumonia and acute pyelonephritis), undetermined febrile syndrome or intestinal perforation associated with simultaneous colonic involvement by lymphoma.

Some form of immunosuppression was present in 12/36 (33.3%) patients, most commonly from chronic infection with human immunodeficiency virus (HIV) in 5/12 patients, followed by renal transplantation (2/12), liver transplantation (2/12), chemotherapy for breast malignancy (1/12), biological therapy with golimumab (1/12) and bone marrow aplasia (1/12).

Most patients had negative serologies for HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV). The presence of chronic infection with HIV, HBV

TABLE 1. Clinical, pathological and radiological characteristics of the patients.

Characteristics	N (%)
Age, mean (years)	56.6
Gender	
Male	21 (58%)
Female	15 (42%)
Classification of lymphoma	
Primary	3 (8.3%)
Secondary	33 (91.7%)
Histological subtype	
Diffuse large B-cell lymphoma	12 (33.3%)
Hodgkin lymphoma	7 (19.4%)
Burkitt lymphoma	4 (11.1%)
T-cell lymphoma	4 (11.1%)
Small lymphocytic lymphoma	3 (8.3%)
Splenic marginal zone lymphoma	3 (8.3%)
Lymphoplasmacytic lymphoma	1 (2.8%)
Follicular lymphoma	1 (2.8%)
High-grade B-cell lymphoma, NOS	1 (2.8%)
Clinical manifestations	
Fever	16 (44.4%)
Lymphadenopathy	16 (44.4%)
Weight loss	15 (41.7%)
Fatigue	15 (41.7%)
Night sweats	12 (33.3%)
Abdominal disconfort	9 (25%)
Back pain	5 (13.9%)
Anorexia	3 (8.3%)
Jaundice	2 (6.1%)
Asymptomatic	3 (8.3%)
Radiological presentation pattern (N=34)	
Solitary nodule	9 (26.5%)
Multiple nodules	14 (41.2%)
Diffuse infiltration	11 (32.4%)
Other imaging findings (N=34)	
Splenomegaly	24 (76.5%)
Hepatomegaly	23 (67.5%)
Pleural effusion	12 (35.3%)
Portal vein thrombosis	2 (5.9%)

and HCV was detected in 5/34 (14.7%), 2/35 (5.7%) and 2/35 (5.7%) cases, respectively. The presence of Epstein-Barr virus (EBV) in liver tissue was detected in two cases, including one diffuse large B-cell lymphoma and one Hodgkin's lymphoma.

Laboratory testing

Liver enzyme tests showed abnormalities in 33/36 (91.7%) patients, including cytolysis in 26/36 (72.2%), cholestasis in 31/36 (86.1%) and hyperbilirubinemia in 11/36 (30.6%). Elevated aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) were detected in 26/36 (72.2%) patients, usually up to 2 to 4-fold the upper limit of normal (ULN), although in 3/26 patients their level was increased more than 10-fold. Most patients had a predominant increase in AST in 15/26 (57.7%) cases. Gamma-glutamyl transferase (GGT) levels were variable from normal (4/36) to up to 2 to 4-fold ULN (13/36), 5 to 10-fold ULN (10/36) or more than 10-fold ULN (9/36) and were more markedly elevated than alkaline phosphatase (ALP). ALP was more often normal (13/36) and most elevations were in the range of 2 to 4-fold ULN (18/36). Bilirubin levels were normal in most (25/36) patients, although those who presented with hyperbilirubinemia (11/36) often presented a marked rise in total bilirubin (6 to 12-fold ULN), usually from conjugated hyperbilirubinemia (10/11). Hypoalbuminemia was detected in 25/36 (69.4%) patients.

Abnormal blood cell counts were detected in 35/36 (97.2%) patients, most commonly anemia (88.9%), thrombocytopenia (50%), leukopenia (44.4%) and leukocytosis (16.7%). Lactate dehydrogenase (LDH) was elevated in 25/36 (69.4%) patients and C-reactive protein (CRP) in 33/36 (91.7%). Coagulation abnormalities were detected in 15/36 (41.7%) patients.

Tumor markers, including alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) and CA 19.9 were within normal range in most patients. Elevated levels of CEA and CA 19.9 were found in only 3/12 and 4/11 patients who were tested, respectively, whereas elevated AFP levels were not found in any of 15 patients tested. In contrast, beta-2 microglobulin, a common marker of lymphoproliferative diseases, was elevated in all patients tested (19/19) with a mean value of 6822 ug/mL (range 1564–30745).

The patients with secondary lymphoma presented significantly higher mean levels of leukocyte count (17.537 vs 0.995 x 10^9/L, P=0.046), AST (227.40 vs 13.86 U/L, P=0.044) and CRP (69.10 vs 17.73 mg/L, P=0.008) than those with primary lymphoma. No significant differences were found regarding ALT, GGT, ALP, bilirubin, LDH or beta-2 microglobulin.

Radiological findings

CT scan was performed in 34 patients and radiological findings were variable and heterogeneous including a single nodule in 9 (26.5%) patients, multiple nodules in 14 (41.2%) and diffuse infiltration in 11 (32.4%) (FIGURE 1). Among those with multiple nodules, the disease manifested either as a relatively limited number of two or three nodules (in four and two patients, respectively) or as a miliary pattern characterized by multiple small discrete nodules

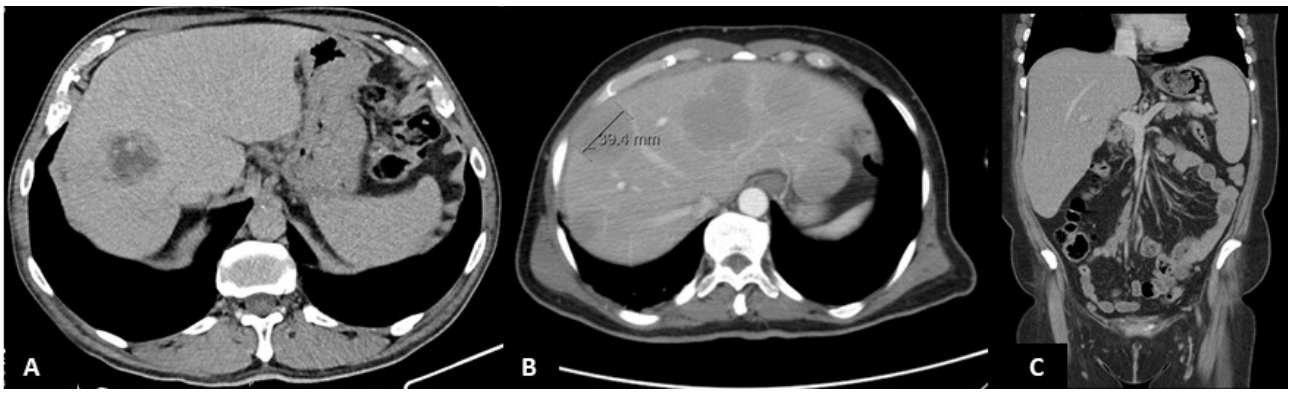

FIGURE 1. Three radiological presentation patterns of hepatic infiltration by lymphoma were identified, including: A. Uninodular, characterized by a solitary nodule. B. Multinodular, characterized by more than one nodule. C. Diffuse infiltration, where the liver is enlarged but no individualized nodules are found.

(in eight patients). The mean diameter of nodules (including solitary nodules or the dominant nodule in those with more than one) was 42.4 mm and they were more commonly located in right lobe in 10 (43.5%) patients, involving both right and left lobes in 9 (39.1%) or limited to left lobe in 4 (17.4%).

Difficulties in differential diagnosis with more common causes of liver nodules were occasionally described. Three patients presenting with a single liver nodule had imaging features suggestive of hepatocellular carcinoma in non-cirrhotic liver and therefore undergone image-guided liver biopsy that unexpectedly revealed a lymphoma. Liver metastases from unknown primary origin were also suspected in five patients presenting with multiple liver nodules and enlarged lymph nodes; as no primary cancer was discovered after thorough diagnostic work-up, they ultimately undergone liver biopsy that revealed an underlying lymphoma. In the remaining patients, the diagnosis of hepatic lymphoma was already suspected either because the patient already carried a previous diagnosis of systemic lymphoma or because associated constitutional symptoms, lymphadenopathy and/or hepatosplenomegaly raised that suspicion; in these cases, liver biopsy was performed for diagnostic and/or staging purposes which would influence therapeutic decisions.

Other abnormal findings included splenomegaly (76.5%), hepatomegaly (67.5%), pleural effusion (35.3%) and portal vein thrombosis (5.9%). In 8/34 (22.2%) the spleen exhibited heterogeneous areas indicative of involvement by lymphoma.

Pathological findings and staging

According to the WHO classification, the most common histological subtype was diffuse large B-cell lymphoma in 12/36 patients (33.3%), followed by Hodgkin's lymphoma (19.4%), Burkitt lymphoma (11.1%), T-cell lymphoma (11.1%), chronic lymphocytic leukemia/small lymphocytic lymphoma (8.3%), splenic marginal zone lymphoma (8.3%), lymphoplasmacytic lymphoma (2.8%), follicular lymphoma (2.8%) and high-grade B-cell lymphoma not otherwise specified (2.8%).

Three types of lymphocytic growth patterns, in terms of portal, nodular and sinusoidal infiltration were documented. The nodular infiltration pattern was the most common tumor growth pattern in 17/36 (47.2%) cases, followed by portal infiltration in 15/36 (41.7%) and sinusoidal infiltration in only 4/36 (11.1%). Fisher-Freeman-Halton exact test revealed that different subtypes of lymphoma exhibited a statistically significant predisposition for certain types of infiltration by neoplastic lymphocytes (P=0.005) (TABLE 2). Most cases of diffuse large B-cell lymphoma demonstrated a nodular growth pattern (8/12) followed by portal (3/12) and sinusoidal (1/12). All cases of Burkitt lymphoma (4/4) demonstrated nodular growth pattern and all cases of T-cell lymphoma demonstrated portal growth pattern (4/4).

TABLE 2. Histological infiltration patterns according to subtype of lymphoma.

Type of lymphoma	Nodular	Portal	Sinusoidal
Diffuse large B-cell lymphoma	8	3	1
Hodgkin lymphoma	3	4	0
Burkitt lymphoma	4	0	0
T-cell lymphoma	0	4	0
Small lymphocytic lymphoma	0	1	2
Splenic marginal zone lymphoma	0	2	1
Lymphoplasmacytic lymphoma	1	0	0
Follicular lymphoma	1	0	0
High-grade B-cell lymphoma, NOS	0	1	0
Total	**17**	**15**	**4**

There was involvement of distant lymph nodes in 25/36 (69.5%) of patients, as determined by histopathological examination or CT evidence of lymphadenopathy with malignancy-associated features. Bone marrow biopsy was performed in 26/36 patients, with confirmation of bone marrow involvement by the lymphoproliferative disease in 19 (52.8%). Splenic involvement was detected in a total of 15 (41.6%) patients, with histological confirmation in 7/15 and suggestive CT findings in the remaining. Other organs, including kidney, lung, bone, adrenal gland, stomach, small bowel, colon, central nervous system and abdominal wall were occasionally involved.

Treatment and follow-up

Treatment strategies were selected according to clinical profile, histological subtype and systemic involvement. Most patients received chemotherapy, which was administered to a total of 29 patients, with complete response in 51.5%, partial response in 13.8% and absence of response in 34.5%. The recurrence rate after complete response was 26.7% and the mean time interval between diagnosis and recurrence was 35.50 months. Additionally, splenectomy was required in seven patients because of hypersplenism and splenic involvement was confirmed in all these patients. In seven patients treatment was not started, either because of rapid disease progression or absence of clinical indication (for example, indolent low-grade lymphoma).

Mean follow-up duration was 35.67 months (range 0–127). During follow-up, 20 patients died, which translates into a mortality rate of 55.6%. Absence of response to treatment (OR=19.57, P<0.001) was significantly associated with higher risk of mortality. The mean level of CRP was also significantly higher in patients who died compared to patients who survived (91.60 vs 43.28 mg/L, P=0.031). In contrast, the presence of night sweats (OR=0.14, P=0.009) and fatigue (OR=0.20, P=0.023) were significantly associated with lower mortality. No significant association was found regarding age, gender, histological subtype, liver function tests or systemic involvement.

DISCUSSION

Hepatic lymphoma is a rare disease that can be categorized as primary when confined to the liver without involvement of the spleen, lymph nodes, peripheral blood, bone marrow or other tissues until at least 6 months after diagnosis or, more commonly, secondary when liver involvement results from systemic spread of disease[11]. Although the liver contains lymphoid tissue, host factors make it a poor environment for the development of malignant lymphoma[12]. Nevertheless, its incidence has increased from 0.021/100,000 person-years in 1975 to 0.122/100,000 person-years in 2016[1]. This is probably related to improvements in early detection and reflects an overall increasing trend in incidence of all cases of lymphoma. In fact, epidemiological studies show that the overall Hodgkin lymphoma incidence rate has been increasing for the past decade, especially among female, young and Asian populations[13], and similar increasing trends have also been reported for non-Hodgkin lymphoma[14].

Although hepatic lymphomas can occur at any age, they are more common in white males aged 50–60 with a male-to-female ratio of 2-3:1[1,2] and are more commonly secondary with a ratio of primary to secondary liver lymphoma close to 1:10[15]. These demographic characteristics are consistent with our results where we also report male predominance and peak incidence during 6th decade of life, with only three cases of primary hepatic lymphoma and 33 cases of secondary hepatic lymphoma. The most common type of lymphoma was diffuse large B-cell lymphoma, consistent with previous studies[15,16].

The clinical manifestations of hepatic lymphomas are usually non-specific and may include fever, night sweats, weight loss or abdominal pain[17]. The most common physical finding is hepatomegaly, which occurs in 75% of patients. Jaundice is rare and present in less than 5% of patients[18]. Rarely, the disease may have acute presentations including abdominal pain[19] or acute liver failure[20]. In our series the classic B-cell symptoms (fever, weight loss, night sweats) were commonly reported. Other manifestations included lymphadenopathy and constitutional symptoms including asthenia or anorexia. Intriguingly, night sweats and asthenia appeared to predict higher likelihood of survival, perhaps related to more prompt seeking healthcare and earlier diagnosis, although these results must be interpreted with caution considering the small sample size.

Laboratory test results are impaired in most patients suffering from hepatic lymphoma. Abnormal liver enzymes (ALT, AST) can be seen as well as elevated LDH. Cholestasis enzymes (GGT, ALP and bilirubin) are sometimes altered as well. Tumor markers such as AFP or CEA tend to be between normal values[21]. We found higher levels of leukocytes, AST and CRP in patients with secondary than primary hepatic lymphoma. A retrospective study reported higher levels of LDH in secondary than primary hepatic lymphoma[16], although we did not find such association, perhaps related to a lower number of primary lymphomas in our study.

A relationship with chronic infection with HCV[22] or HBV has been reported[23]. It is possible that chronic antigenic stimulation by HBV may lead to the development of lymphoproliferative disease. Some reports support the theory that HCV can infect reactive and neoplastic B cells, and that persistent HCV infection may induce primary hepatic as well as other organ B cell lymphomas that may secondarily infiltrate liver[24], with possible regression after HCV eradication[25]. In our series, chronic HBV and HCV infection was found in two patients each, supporting a potential pathogenic role in the development of hepatic lymphomas.

Impaired immune surveillance, such as acquired immunodeficiency syndrome[26] or transplant recipients[27], also seems to be linked to some cases of primary hepatic lymphoma. In our series, approximately one-third of cases occurred in immunosuppressed patients and specifically 2/3 cases of primary liver lymphoma were diffuse large B-cell lymphoma that occurred after liver transplantation. These cases are often associated with EBV infection[28]. We also found two cases of EBV-associated lymphomas, including one diffuse large B-cell lymphoma and one Hodgkin's lymphoma. Therefore, immunosuppression and opportunistic infection with oncogenic viruses appears to be an important risk factor for liver lymphomas.

Lymphomatous liver involvement can have a wide range of radiological presentations. It can present as a solitary mass or as multiple lesions (with or without a dominant lesion), or even in a miliary pattern characterized by multiple small discrete nodules. Other patterns include diffuse infiltration (with or without hepatomegaly) or, rarely, portal vein thrombosis in periportal lymphoma. Primary hepatic lymphoma usually presents as an heterogeneous solitary mass in approximately 60% of cases or as multiple lesions, usually with a dominant nodule, in 35–40%, whereas secondary liver lymphomas typically present as diffuse infiltration or multifocal homogeneous lesions along with signs of extrahepatic disease[4].

Hepatic lymphomas have three main histological types of infiltration: portal, nodular or sinusoidal, as previously described[9]. In our study, the most common type of infiltration was nodular, followed by portal and sinusoidal. Another study reported similar relative frequencies for each type of growth pattern (nodular: 76%, portal: 14%, sinusoidal: 10%)[15]. We additionally demonstrated that certain types of lymphoma appear to have a predilection for specific infiltration patterns, such as diffuse large B-cell lymphoma and Burkitt lymphoma which appear to have a predilection for nodular infiltration whereas T-cell lymphoma preferentially exhibits portal growth pattern. Prospective studies are needed to confirm these findings, which could provide important diagnostic clues.

In our study, most patients were treated with chemotherapy. Current literature favors combination chemotherapy as the frontline treatment for its least invasiveness and improved survival. Favorable prognosis of primary liver lymphoma can be obtained by early surgery combined with chemotherapy. In cases of resectable disease, an aggressive surgical approach with postoperative chemotherapy in selected patients leads to increased long-term survival[29]. Solitary lesions should be considered as the best candidates for radical hepatectomy. Unfortunately, a mere minority of patients is eligible to undergo surgical intervention[30]. Radiation therapy before chemotherapy may also be considered when patients present with hyperbilirubinemia that precludes chemotherapy[31]. Therefore, the importance of multidisciplinary approach involving gastroenterologists, surgeons, hemato-oncologists, pathologists and radiologists cannot be overemphasized.

Hepatic lymphoma is associated with poor prognosis, with reported 3- and 5-year overall survival of 43.5% and 39.2%, respectively[1], although survival has improved during the last two decades, probably as a result of more widespread use of rituximab[32]. Therefore, although incidence has increased over the last decades, mortality has remained stable[1]. In our study, higher levels of CRP and absence of complete response to treatment appeared to be associated with higher mortality risk whereas night sweats, asthenia and higher levels of CEA appeared to be protective, although these results must be interpreted with caution considering the small sample size. Older age, black race, diffuse large B-cell lymphoma and advanced stage disease have been reported as independent predictors of worse survival[1]. An association of higher levels of AST with poor outcomes

was also noted[8]. Another retrospective study also reported worse survival for secondary compared to primary liver lymphoma[16]. Nevertheless, in our study, an association with age, liver enzyme tests, histological subtype or involvement of other organs was not found.

Its retrospective single-center design and small sample size are limitations of our study. Also, the fact that most cases represent hepatic involvement by systemic lymphoma results in a high proportion of cases representing an advanced stage disease where liver infiltration is *per se* an adverse prognostic factor that may be a confounding factor to determine other prognostic factors. Nevertheless, our study also has strengths. In contrast to larger studies based in limited and often inaccurate data retrieved from national healthcare databases[1,2,32], we extensively reviewed the electronic medical records from each patient and therefore there is less missing information and our data are more complete and accurate. Besides, in comparison with other studies that performed a retrospective analysis based in revision of medical records[8,15,16], we describe the largest series of hepatic lymphomas to date. Therefore, we believe our study provides important information related to hepatic lymphomas in a real-life setting that could lead to improvements in diagnostic and management strategies. As the medical world gets more familiar with hepatic lymphomas, early recognition and timely proper management will certainly result in improved clinical outcomes.

In conclusion, liver lymphoma is an important differential diagnosis for solitary or multiple liver nodules that requires a high index of clinical suspicion. Different types of lymphoma may infiltrate the liver, whether primarily when confined to this organ or, more commonly, secondarily as part of systemic disease. An accurate histopathological classification and complete staging are essential to define the best management strategy and increase chances of survival.

Authors' contribution

Material preparation, data collection and analysis were performed by Dias E, Gonçalves R and Cardoso P. The first draft of the manuscript was written by Dias E and all authors commented on previous versions of the manuscript. All authors contributed to the study conception and design and read and approved the final manuscript.

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RESUMO – Contexto – A incidência de linfoma hepático tem aumentando recentemente e o diagnóstico pode ser desafiante, na medida em que a apresentação clínica e os achados imagiológicos são geralmente variáveis e inespecíficos. **Objetivo –** Os objetivos deste estudo foram descrever suas principais características clínicas, patológicas e de imagem e identificar fatores de mau prognóstico. **Métodos –** Foi realizado um estudo retrospetivo que incluiu todos os pacientes com diagnóstico histológico de linfoma hepático num período de 10 anos no nosso centro. **Resultados –** Foram identificados 36 pacientes, com média de idade de 56,6 anos e predomínio de género masculino (58%). Havia três pacientes com linfoma hepático primário (8,3%) e 33 com linfoma hepático secundário (91,7%). O tipo histológico mais comum foi o linfoma difuso de grandes células B (33,3%). As manifestações clínicas mais comuns incluíram febre, linfadenopatia, emagrecimento, hipersudorese noturna e desconforto abdominal; 3 (11,1%) pacientes eram assintomáticos. A tomografia computadorizada revelou padrões radiológicos heterogêneos, incluindo um único nódulo (26,5%), múltiplos nódulos (41,2%) ou infiltração difusa (32,4%). A taxa de mortalidade durante o seguimento foi de 55,6%. Níveis mais elevados de proteína C reativa (P=0,031) e ausência de resposta ao tratamento (P<0,001) foram significativamente associados a maior mortalidade. **Conclusão –** O linfoma hepático é uma doença rara que pode envolver o fígado como parte de uma doença sistêmica ou, menos comumente, estar confinado a este órgão. A apresentação clínica e os achados radiológicos são frequentemente variáveis e inespecíficos. Associa-se a elevada mortalidade e fatores de mau prognóstico incluem níveis mais elevados de proteína C reativa e ausência de resposta ao tratamento.

Palavras-chave – Linfoma hepático; fígado; biópsia hepática; nódulo hepático.

REFERENCES

1. Qiu MJ, Fang XF, Huang ZZ, Li QT, Wang MM, Jiang X, et al. Prognosis of primary hepatic lymphoma: A US population-based analysis. Transl Oncol. 2021;14:100931.
2. Zhang SL, Chen C, Rao QW, Guo Z, Wang X, Wang ZM, et al. Incidence, Prognostic Factors and Survival Outcome in Patients With Primary Hepatic Lymphoma. Front Oncol. 2020;10:750.
3. Silva JM, Saraiva RO, Simões G, Araújo C, Calinas F, Coimbra J. Primary Liver Lymphoma Presenting as Liver Nodules. GE Port J Gastroenterol. 2021;28:134-8.
4. Alves AMA, Torres US, Velloni FG, Ribeiro BJ, Tiferes DA, D'Ippolito G. The many faces of primary and secondary hepatic lymphoma: imaging manifestations and diagnostic approach. Radiol Bras. 2019; 52:325-30.
5. Imrani K, Znati K, Amouri W, Nassar I, Billah NM. Primary hepatic lymphoma in liver cirrhosis: A rare case report. Radiol Case Rep. 2021;16:2179-83.
6. Bohlok A, De Grez T, Bouazza F, De Wind R, El-Khoury M, Repullo D, et al. Primary Hepatic Lymphoma Mimicking a Hepatocellular Carcinoma in a Cirrhotic Patient: Case Report and Systematic Review of the Literature. Case Rep Surg. 2018;2018:9183717.
7. Forghani F, Masoodi M, Kadivar M. Primary Hepatic Lymphoma Mimicking Cholangiocarcinoma. Oman Med J. 2017;32:335-8.
8. El-Sharkawi D, Ramsay A, Cwynarski K, Hughes D, Prentice A, Davies N, et al. Clinico-pathologic characteristics of patients with hepatic lymphoma diagnosed using image-guided liver biopsy techniques. Leuk Lymphoma. 2011;52:2130-4.
9. Loddenkemper C, Longerich T, Hummel M, Ernestus K, Anagnostopoulos I, Dienes HP, et al. Frequency and diagnostic patterns of lymphomas in liver biopsies with respect to the WHO classification. Virchows Arch. 2007;450:493-502.
10. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:2375-90.
11. Ippolito D, Porta M, Maino C, Pecorelli A, Ragusi M, Giandola T, et al. Diagnostic approach in hepatic lymphoma: radiological imaging findings and literature review. J Cancer Res Clin Oncol. 2020;146:1545-58.
12. Dantas E, Santos J, Coelho M, Sequeira C, Santos I, Cardoso C, et al. Primary hepatic lymphoma in a patient with cirrhosis: a case report. J Med Case Rep. 2020;14:168.
13. Huang J, Pang WS, Lok V, Zhang L, Lucero-Prisno DE, Xu W, et al. Incidence, mortality, risk factors, and trends for Hodgkin lymphoma: a global data analysis. J Hematol Oncol. 2022;15:57.
14. Schmitz-Feuerhake I, Frentzel-Beyme R, Wolff R. Non-Hodgkin lymphomas and ionizing radiation: case report and review of the literature. Ann Hematol. 2022;101:243-50.
15. Bai YF, Liu JM, Zhang XM, Jiang CZ, Xu X, Zheng SS. Percutaneous liver biopsy: retrospective study of primary and secondary hepatic lymphoma in twenty-one patients. Hepatobiliary Pancreat Dis Int. 2017;16:58-64.
16. Peng Y, Qing AC, Cai J, Yue C, French SW, Qing X. Lymphoma of the liver: Clinicopathological features of 19 patients. Exp Mol Pathol. 2016;100:276-80.
17. Noronha V, Shafi NQ, Obando JA, Kummar S. Primary non-Hodgkin's lymphoma of the liver. Crit Rev Oncol Hematol. 2005;53:199-207.
18. Padhan RK, Das P, Shalimar. Primary hepatic lymphoma. Trop Gastroenterol. 2015;36:14-20.
19. Abdelrahim WE, Mohamed KE, Mekki SO, Saad EA. Primary Hepatic Lymphoma Presenting as an Acute Abdomen in a Young Female Patient: A Case Report and Literature Review. Case Rep Surg. 2019;2019:6784325.
20. Romacho López L, León Díaz FJ, Sánchez Pérez B, Pérez Daga JA, Fernández Aguilar JL, Montiel Casado MC, et al. Acute Liver Failure Caused by Primary Non-Hodgkin's Lymphoma of the Liver. Transplant Proc. 2016;48:3000-2.
21. Martínez DTE, Sánchez-Chica PA, Del Valle Loarte P, Ganoza GEC, Pérez-González M, Vázquez-Echarri J, et al. Primary Hepatic Lymphoma: the Importance of Liver Biopsy. J Gastrointest Cancer. 2017;48:373-5.
22. Bronowicki JP, Bineau C, Feugier P, Hermine O, Brousse N, Oberti F, et al. Primary lymphoma of the liver: clinical-pathological features and relationship with HCV infection in French patients. Hepatology. 2003;37:781-7.
23. Mrabet S, Zaghouani H, Mestiri S, Akkari I, Ben Jazia E. Primary Hepatic Lymphoma in a Patient with Chronic Hepatitis B. Case Rep Gastroenterol. 2020;14:632-6.
24. Somaglino C, Pramaggiore P, Polastri R. Primary hepatic lymphoma in a patient with chronic hepatitis B and C infection: diagnostic pitfalls and therapeutic challenge. Updates Surg. 2014;66:89-90.
25. Oda Y, Kou T, Watanabe M, Sakuma Y, Taguchi N, Kato Y, et al. Regression of B-cell lymphoma of the liver with hepatitis C virus infection after treatment with pegylated interferon-alpha and ribavirin. Dig Dis Sci. 2010;55:1791-3.
26. Widjaja D, AlShelleh M, Daniel M, Skaradinskiy Y. Complete remission of primary hepatic lymphoma in a patient with human immunodeficiency virus. World J Clin Cases. 2015;3:186-90.
27. Muttillo EM, Dégot T, Canuet M, Riou M, Renaud-Picard B, Hirschi S, et al. Primary Hepatic Lymphoma After Lung Transplantation: A Report of 2 Cases. Transplant Proc. 2021;53:692-5.
28. Tsuji H, Yoshifuji H, Shindo T, Hishizawa M, Ishida A, Fujimoto M, et al. Primary hepatic lymphoma as other iatrogenic immunodeficiency-related lymphoproliferative disorders: a case report and review of the literature. Mod Rheumatol Case Rep. 2021;5:172-7.
29. Yang XW, Tan WF, Yu WL, Shi S, Wang Y, Zhang YL, et al. Diagnosis and surgical treatment of primary hepatic lymphoma. World J Gastroenterol. 2010;16:6016-9.
30. Mastoraki A, Stefanou MI, Chatzoglou E, Danias N, Kyriazi M, Arkadopoulos N, et al. Primary hepatic lymphoma: dilemmas in diagnostic approach and therapeutic management. Indian J Hematol Blood Transfus. 2014;30:150-4.
31. Tammana VS, Begum R, Oneal P, Karpurapu H, Muley A, Yeruva SL, et al. A novel use of early radiation therapy in the treatment of hyperbilirubinemia in a patient with primary hepatic lymphoma and chronic hepatitis C. Case Rep Gastrointest Med. 2014;2014:724256.
32. El-Fattah MA. Non-Hodgkin Lymphoma of the Liver: A US Population-based Analysis. J Clin Transl Hepatol. 2017;5:83-91.