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Reappraisal of primary hepatic lymphoma: Is surgical resection underestimated?

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ABSTRACT

Primary hepatic lymphoma (PHL) is defined as a lympho-proliferative disorder limited to the liver without any involvement of the spleen, lymph nodes, bone marrow or blood. Diffuse large B-cell lymphoma (DLBCL) is the most common histological type counting more than 60–80% of all PHL. Usually, it occurs in middle-aged men with aspecific symptoms and diagnosis is confirmed by histopathology. In order to expand current knowledge and to investigate an optimal therapeutic strategy, a systematic review of literature was conducted in February 2016. A total of 274 articles were retrieved, and after exclusion, 55 were retained, reporting 147 cases of PHL. Patients were mainly men (64.9%) with a median age at diagnosis of 57 years (range: 17–92) and right hepatic lobe involvement (69.6%). Among the 147 patients, 9% received no therapy while 77% underwent treatment including chemotherapy, surgery and radiotherapy in 64%, 26% and 1% of cases, respectively. Mean follow-up was 22.6 months (range: 0.2–360). Overall mortality was 29.2% with a 90-day mortality of 26%. Risk factors for increased mortality include; bilobar lesions ($p = 0.001$), right lobe localisation ($p = 0.003$) and non-surgical approach or the absence of any treatment ($p = 0.001$). A trend towards favourable outcomes for young patients (mean = 50.4 years) with a large liver lesion was achieved by surgical management of PHL but this did not achieve statistical significance. Statistical analysis indicates that in cases of resectable disease, an aggressive surgical approach in selected patients leads to increase long-term survival. Thus, two hypotheses should be assessed in further randomized studies: 1°) resectable PHL is a less severe form or 2°) hepatectomy is an effective treatment for PHL.

1. Introduction

Primary hepatic lymphoma (PHL) is a rare disease (Noronha et al., 2005), reported as reaching approximately 0.016% of all cases of Non-Hodgkin Lymphoma (NHL). It was first defined in 1998 when Lei (1998) described commonly accepted criteria for PHL after reviewing 90 cases from 1981 to 1993. These were: 1) Initial symptoms related to liver involvement; 2) Absence of organ involvement, (including lymph nodes and bone marrow); 3) Absence of abnormal cells in the peripheral blood smear. PHL that is predominantly of B-cell origin accounts for most clinical and pathological features within case studies published.

As the most common form of NHL, diffuse large B-cell lymphoma (DLBCL) is a rapidly growing cancer accounting for up to 30% of newly diagnosed cases in the United States (Armitage, 2012). DLBCL potentially arises within lymph nodes and areas such as in the gastro-intestinal tract. As the largest reticulo-endothelial organ, DLBCL can develop in the liver. This occurs via sequential adhesive interactions of human B cells with hepatic sinusoidal endothelial cells (HSECs) and subsequent proliferation within the liver (Shetty et al., 2012..

Currently, some risk factors have been reported. Patients with hepatitis C virus (HCV) infection or immunosuppressive disorders (systemic lupus erythematosus, acquired immune deficiency syndrome, those receiving immunosuppressive treatment, etc.) are more likely to present with such disease (Page et al., 2001).

Like most rare conditions, no specific recommendation has been

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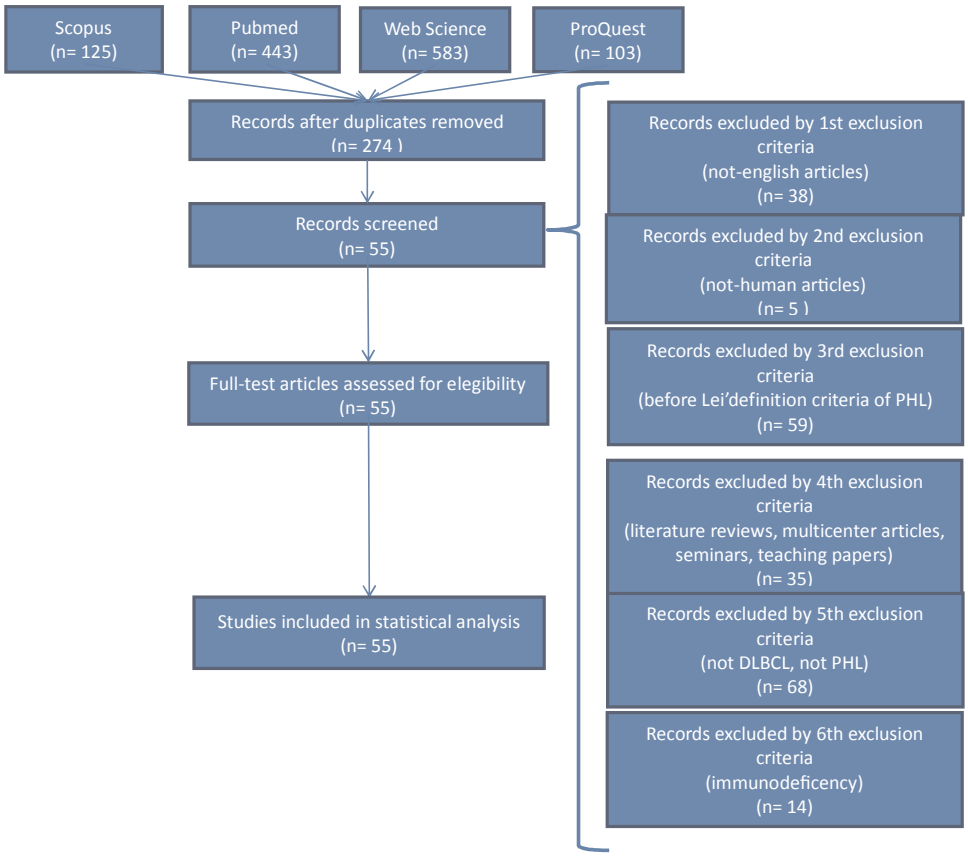

Fig. 1. Literature review flow-charts.

proposed for PHL. The United States National Comprehensive Cancer Network recommends managing DLBCL with rituximab, cyclophosphamide, adriamycin, vincristine and prednisone (R-CHOP protocol) with a complete remission rate of 83.3%. Still, multiple therapeutic options have been reported, including surgery, chemotherapy, radiation or combinations of the above modalities without specific outcome data (Zelenetz et al., 2013).

In order to identify prognostic factors and assess therapeutic regimens for PHL, we performed a systematic literature review of all published cases of PHL (DLBCL type) in non-immunocompromised patients. Herein are reported results of this analysis.

2. Material and methods

The literature search was performed in Medline, Web Science, ProQuest and Scopus libraries in February 2016 by two authors (MC, LS).

Restrictions applied during the search strategy were regarding publication date and language (article before Lei PHL definition in 1998 (Lei, 1998) and non-english language articles were excluded) owing to the lack of unanimity in diagnostic criteria before 1998. MeSHs for the search are: "primary", "liver", "hepatic" and "lymphoma". The search was restricted to human studies. Titles and abstracts were screened for relevance by two authors (MC, LS) independently.

Histological diagnosis was achieved according to the World Health Organization classification (Swerdlow et al., 2008). Due to different prognosis of all PHL phenotypes, all full-text articles evaluating DLBCL (the most common type of B-cell lymphoma, the predominant PHL type) were included. Articles reporting series with different types of PHL were examined and all data regarding DLBCL were considered. Reviews and congress abstracts were excluded to avoid redundancy of data. Due to the paucity of data, case reports were included in the research. Any discrepancies were resolved in a consensus meeting with a third author (AZLB) and two methodologists (ML and CR). Two authors (LS and ML) independently extracted means, medians and standard deviations (SD) of data gained.

In order to establish diagnosis of PHL the following were required: 1) A surgical specimen/excisional liver biopsy providing enough material for formalin-fixed samples with minimal immunohistochemistry (CD45, CD20, and CD3) (DLBCL immunophenotype includes positivity for some or all of the pan–B cell markers, usually including CD19, CD20, and/or CD79a. In practice, DLBCL was also diagnosed by morphology and positivity for CD20, a mature B-cell marker and, in rare cases when CD20 was negative, the pan–B-cell marker CD79a was used (Hunt and Reichard, 2008)). 2) Complete blood test excluding leukemic cells in the peripheral blood. 3) At least an imaging study such as thoraco-abdominal computed tomography (CT) scan or magnetic resonance imaging (MRI) or ultrasonography (US). 4) A bone marrow aspirate and biopsy.

The following variables were extracted from each study; demographic data (number of patients, age, gender), symptoms at diagnosis (pain, fever, fatigue, etc), hepatitis virus (B and/or C), localization of PHL (right lobe, left lobe, bilobar), number of lesions (single or multiple lesions), maximum diameter of the lesion, imaging characteristics (CT, MRI, US studies), biopsy, primary suspected diagnosis, treatment, immunohistochemical DLBCL markers (CD 20, CD 45, LCA), mortality (overall, early and late) and overall survival. Early mortality was defined as death occurring during the 90 days following the diagnosis.

Descriptive statistical analysis, including mean and standard deviation for continuous variables, and count and percentage for categorical variables, was performed. Student *t*-test was used for continuous variables and Fisher's exact test was used for categorical variables. Treatment patterns and survival were assessed from diagnosis until death or last follow-up. Overall survival (OS) was defined as the interval from the diagnosis to the last visit or death. The curves for OS were constructed using the Kaplan-Meier method and compared using