

Successful hemihepatectomy following chemotherapy for primary liver lymphoma: case report and review of literature

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ABSTRACT: Non-Hodgkin lymphomas (NHL) comprise a heterogeneous group of B-cell and T-cell neoplasms. Diffuse large B-cell lymphoma (DLBCL), the most common type of NHL, accounts for around 30-40% of NHL cases. However, primary hepatic location of NHLs is rare and constitutes 0.01% of all NHL cases. Due to this rarity and a lack of large randomized trials, it is still unclear what treatment should be used for primary hepatic DLBCLs. In this study, we report of a female patient with primary hepatic DLBCL who was successfully treated with neoadjuvant chemotherapy and surgery. We also shortly review the literature regarding surgical treatments for primary GI tract NHLs. Taking into account our experience and the current literature, surgical treatment with post-operative chemotherapy seems to be a feasible option for patients with focal primary hepatic DLBCLs.

KEYWORDS: Non-Hodgkin's lymphoma, hepatic DLBCL, hemihepatectomy, treatment

INTRODUCTION

Non-Hodgkin lymphomas (NHL) comprise a heterogeneous group of B-cell and T-cell neoplasms that typically develop in the lymph nodes. Diffuse large B-cell lymphoma (DLBCL), the most common type of NHL, accounts for around 30-40% of NHL cases. In general, NHLs account for 3.4% and around 3.06% of cancer-related deaths in the US [1,2,3] and Europe [4], respectively; with an approximate incidence rate of 3-4/100000/year [3]. Because of a surge in NHL incidence, there is extensive research regarding more efficient treatments for NHLs [5,6,7]. While chemotherapy, e.g., the R-CHOP regimen, seems to be a feasible treatment for NHL-like diffuse large B-cell lymphomas located in the lymph nodes, [6,8,9,10] it is still unclear what treatment should be used in patients with relatively aggressive, extranodal NHLs [6,11,12,13,14]. Approximately one-third of NHLs develop outside the lymph nodes, with the gastrointestinal tract being the most common site of primary extranodal DLBCL [2,6]. Despite ample information regarding treatment of primary gastric DLBCLs, such as surgery, radiation therapy, and chemotherapy [15,16,17,18], there is no consensus on managing primary DLBCLs in the GI tract [13, 19, 20, 21]. Hepatic DLBCLs are very rare and account for 0.01% of all NHL cases [22]. There is no universally accepted treatment for hepatic DLBCLs mainly due to a lack of randomized trials and analyses of available treatments. Thus, it is important to reach consensus regarding primary hepatic DLBCL treatment based on the already described cases. In this case report, we present a female patient with primary hepatic DLBCL.

A CASE REPORT

A 45-year-old female patient presented with fatigue, decreased appetite, and unintentional weight loss of 5 kg over 1 month. Laboratory studies revealed iron deficiency anemia (hemoglobin level of 8.2 g/dL, red blood count (RBC) of $3.5 \times 10^6/\mu\text{L}$, hematocrit (HCT)

of 26.4%, erythrocyte sedimentation rate (ESR) of 60mm/1h). Abdominal ultrasound revealed two solid, hypoechoic tumors of unknown etiology; 40mm and 90mm in diameter in the right and left hepatic lobes, respectively. There were no other abnormalities in the abdomen. Upper and lower gastrointestinal tract endoscopy and chest x-ray were noncontributory. Contrast-enhanced computed tomography (CT) displayed (Figure 1) well-defined, hypodense (Hounsfield units were 40-45) liver tumors, 80mm and 90mm in diameter in the right left lobes, respectively. Echinococcus-specific and anti-HCV IgG antibodies and HBs antigen were negative. Serum alpha fetoprotein, carcinoembryonic antigen, aspartate and alanine aminotransferases, alkaline phosphatase, and lactate dehydrogenase were normal.

First, percutaneous, ultrasound-guided needle aspiration biopsy was performed, which revealed cells suspected for malignancy. On this basis, the patient was qualified for surgery with two-stage hepatectomy and portal branch ligation [23]; however, intraoperatively, the tumors were found to be locally unresectable, and we only performed open tumor biopsy, with peripheral and portal blood samples taken for cytometric evaluation of dendritic cells. On histopathology, the tumor was diagnosed as diffuse large B-cell lymphoma, strongly positive for CD20 and with Ki67 equal to 80% on immunohistochemistry. Subsequent bone marrow biopsy revealed cellularity of approximately 80%, with slight rejuvenation, an increased number of normal megakaryocytes, and dispersed normal cells positive for CD20 and CD79.

The patient was treated with one cycle of rituximab, cyclophosphamide, vincristine, doxorubicin hydrochloride, and prednisone (R-CHOP regimen), and showed a partial but significant response. Contrast-enhanced CT demonstrated a 33mm x 50mm x 40mm solid tumor within the right lobe of an enlarged liver, with a well-demarcated margin; the other tumor regressed completely (Figure 2). Subsequently, the patient was qualified for surgery. During the surgery, the tumor was localized, and right hemihepatecto-

my and cholecystectomy were performed. There was no need for blood transfusion, total operative time was 110 min, and the patient was discharged on the 10th postoperative day. The recovery period was uneventful.

Macroscopically, we found a well-circumscribed, fragile, encapsulated tumor with the largest diameter of 33mm. Histologically, diffuse large B-cell lymphoma, partially necrotic, was confirmed. Further immunohistochemical staining was strongly positive for CD20 in tumor cells. Microscopic investigation of the residual part of the right liver lobe revealed lymphocytic infiltrates, small-degree fibrosis, and focal necrosis.

The patient has been followed-up for 3 years and has remained disease-free with no evidence of local recurrence, metachronic primary tumor, or distant metastases.

DISCUSSION

Currently, patients with DLBCL receive mostly the RCHOP chemotherapeutic regimen, which is a globally acknowledged treatment standard [3,6,9] Unfortunately, 40% of patients with DLBCL treated with RCHOP die [3] and therefore more efficient treatments are needed. Some authors put forward that novel chemotherapies for DLBCL, based on RCHOP, should be introduced. Such a novel regimen, dubbed R(X)CHOP, should contain drugs that will improve outcomes. Most investigators add eprazumab, bortezomib, or lenalidomide. Some studies evaluated the efficacy of autologous stem cell transplantation after chemotherapy [24-30]. However, large randomized trials that would confirm the superiority of these regimens over standard RCHOP have not been performed to date [3]. Currently, it is important to combine the approved regimen with other approaches in order to improve patients' survival and quality of life.

It is also crucial to underline the importance of proper prognostic assessment in these patients. As regards extranodal DLBCL as a prognostic factor of survival, some early studies revealed, in univariate analyses, that the GI tract and Waldeyer's ring (WR) localizations were associated with better 5-year overall survival (OS), while in multivariate analyses, no nodal or extranodal site had any had prognostic value [2]. However, more recent studies confirmed better outcomes in patients with DLBCL localized in the WR also in multivariate analyses. Moreover, one study revealed that involvement of pleura, small intestine, peritoneum, adrenal glands, testes, bone marrow, and peripheral blood is associated with worse OS [31]. As regards liver involvement, all studies performed to date have shown that it has no prognostic value. Thus, other potential prognostic factors are studied. Among the most promising prognostic factors, there is FISH detection of MYC, Bcl6, Bcl2 aberrations, absolute lymphocyte count (ALC), serum immunoglobulin free light chains, vitamin D levels, serum cytokines/chemokines, and imaging with positron emission tomography (PET) [3]. However, some methods, e.g., immunohistochemical algorithms or gene expression profiling, are expensive and laborious. Thus, the International Prognostic Index (IPI) and its two derivative prognostic systems, i.e., age-adjusted IPI (aaIPI) and revised IPI, are still widely used. Moreover, although DLBCL was divided into 15 subgroups in the WHO 2008 classification, it seems that this classification does not translate into clinical outcomes. A recent study

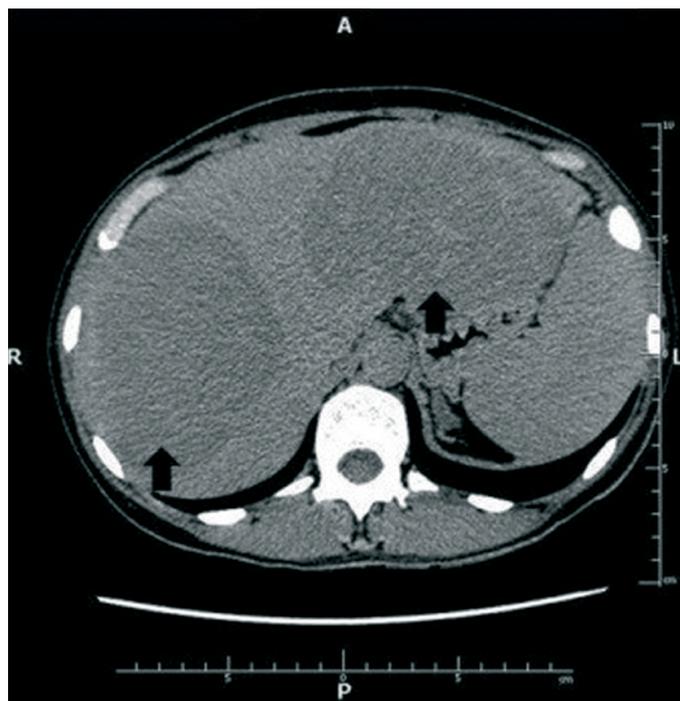


Fig. 1. Before chemotherapy: contrast-enhanced computed tomography revealed well-defined, hypodense liver tumors in the right (80mm) and left (90mm) liver lobes.

[32] revealed that immunohistochemical algorithms that classified gastrointestinal DLBCL into 2 groups, i.e., germinal center B cell-like (GCB) and activated B cell-like (ABC) subtypes, did not predict prognosis. Similarly, Culpin et al. [33] showed that currently used prognostic markers, such as CD10, Bcl-6, Bcl-2, MUM1, Ki-67, CD5, GCET1, FoxP1, LMO2, and algorithms, such as Hans, Hans, Muris, Choi, Choi, Nyman, Visco-Young, Tally, still give controversial results; thus, better markers are needed for clinical practice. Interestingly, according to Emile et al. [19], patients with PHL liver involvement can be divided into two distinct subgroups depending on whether there is nodular or diffuse liver infiltration. Patients with the nodular infiltration had 1-year survival of 70% and 3-year survival of 57%, while patients with diffuse infiltration had 1-year and 3-year survivals of 38% and 18%, respectively. That difference was statistically significant ($p=0.0033$).

With regard to surgical treatment for gastrointestinal DLBCLs, some studies showed promising results. Ding et al. [11] demonstrated that patients ($n=37$) with primary gastrointestinal NHLs treated surgically had 5-year survival of 50%. Moreover, a study performed by the Hellenic Cooperative Oncology Group (HeCOG) [34] showed that surgical treatment is associated with similar outcomes as chemotherapy. In that study, out of 128 primary GI tract NHL cases, 83 patients had complete response (CR) - 43 patients due to surgery and 40 patients due to chemotherapy, respectively. By the time of publishing the results, 76.74% of patients treated surgically and 72.5% of patients treated with chemotherapy remained in CR, respectively. It is also worth noting that 100% of patients after surgical treatment and 62.5% of patients after chemotherapy initially achieved CR, respectively; however, disease stage was the only major prognostic factor. A much larger, multicenter study by Kim et al. [13] compared survival rate of patients with intestinal DLBCL ($n=345$) who were treated with either chemotherapy or surgery, or with both methods. There was a significant difference in 3-year survival between patients who received chemotherapy

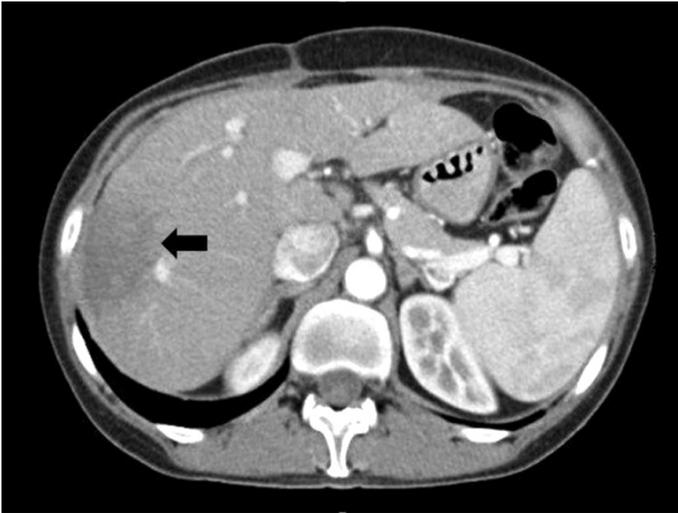


Fig. 2. After chemotherapy and before right hemihepatectomy: contrast-enhanced CT demonstrated a well-demarcated solid tumor (33x50x40mm) within the right lobe of an enlarged liver; the other tumor regressed completely.

only (62%) compared to patients who underwent surgery and subsequent chemotherapy (91%). To our knowledge, there are no published studies that compared the significance of liver involvement with other GI tract localizations. Moreover, most studies that compared survival rates between patients with extranodal DLBCL and nodal DLBCL did not take into account that patients with the former involvement could additionally benefit from surgery followed by chemotherapy. Thus, current knowledge regarding treatment and prognosis in primary hepatic lymphomas (PHL) is derived mostly from case reports and small studies [20]. Lei [35] was one of the first authors to analyze PHL epidemiology, treatment options, and survival in 90 patients with PHL. That author described 10 patients who were treated surgically, with median survival of 22 months (range: 1.5-120 months). Although two of those patients experienced disease recurrence respectively 2 months and 8 months following resection, both responded well to salvage chemotherapy. On the other hand, 40 patients who received chemotherapy only had median survival time of 6 months. However, the observed more favorable outcomes in patients treated surgically compared to patients who received chemotherapy could be due to differences in initial characteristics such as better performance status and smaller tumor volume in patients scheduled for surgery. Avlonitis et al. [36] analyzed 14 patients who underwent surgery followed by adjuvant chemotherapy, with median survival of 20.7 months (range: 10-123.6 months); in contrast, the median survival time of patients treated with chemotherapy alone was 14 months. In another retrospective study, Yang et al. [37] described 9 patients (median age of 51.4 years) with PHL who underwent surgical treatment. In five cases, left hemihepatectomy was performed, right hemihepatectomy in three cases, and one patient underwent both. One patient died 8 days after surgery due to hepatic insufficiency. With median survival of 23 months, the cumulative 6-month, 1-year, and 2-year survival rates were

77.8%, 66.7%, and 55.6%, respectively. Moreover, one patient was disease-free >5 years after resection. In univariate analyses, it was revealed that postoperative chemotherapy was the only significant prognostic factor for survival ($p=0.006$). Edit et al. [38] described a 48 year-old female patient with primary hepatic DLBCL (solitary tumor, 1.5 cm in diameter) who received neoadjuvant chemotherapy and then underwent complete tumor resection. After six courses of adjuvant chemotherapy, the patient was alive and well for more than 5 years, with no evidence of tumor recurrence. This case is particularly interesting to us as it clearly shows that surgical resection of hepatic DLBCL with preoperative chemotherapy could lead to favorable outcomes. In a more recent study, Yu et al. [39] described a patient with primary hepatic marginal zone B cell lymphoma who underwent left hemihepatectomy and then received two cycles of the CHOP regimen. After 15 months of follow-up, the patient was alive and well with no signs of disease recurrence. Steller et al. [40] described a 59 year-old female patient with a 10-cm tumor that was diagnosed postoperatively as a primary hepatic DLBCL. After the surgery, the patient received 6 cycles of CHOP-based chemotherapy, which led to good response. After 60 months of follow-up, the patient showed no symptoms or signs of recurrent disease.

CONCLUSIONS

Due to the rarity of PHL, prospective trials and retrospective studies that compare the effectiveness of different treatments are difficult to perform. An analysis of published reviews and case reports indicates that surgical resection with preoperative or postoperative chemotherapy is a feasible treatment for PHL as it led to good outcomes in most patients who received it. It remains unclear whether this strategy would be beneficial to all patients. In most patients older than 60 years of age who generally had poor IPI, surgical resection was not carried out even though PHLs presented as solitary masses. Because in some cases chemotherapy alone can lead to good clinical outcomes, it seems feasible to use it as the only treatment, especially when qualification for surgery is controversial. However, taking into the account published literature and our own experience, it seems that the RCHOP regimen after surgical resection can be recommended for some patients with focal disease.

In conclusion, diffuse large B-cell lymphoma (DLBCL) is extremely rare. As described in our case, preoperative diagnostic difficulties can be conclusively resolved only with a histopathological examination of specimens sampled during surgery. Treatment of hepatic DLBCL is complex and may require close cooperation between various clinicians, such as surgeons and hematologists. Due to an asymptomatic course and advanced disease at diagnosis, technically difficult operations are often necessary. Thus, surgeons who perform surgeries for hepatic DLBCL should be experienced in complex liver surgery.

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