Primary Hepatic Lymphoma Resected by ALPPS Procedure (Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy)

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ABSTRACT

Background: Primary hepatic lymphoma represents a very rare location of non-Hodgkin lymphomas, whose treatment consists of liver tumor resection followed by chemotherapy. In some cases, however, upfront hepatectomy is not feasible due to insufficient volume of the liver remnant.

Case report: An ALPPS (Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy) procedure was performed in a patient with a large primary hepatic lymphoma, whose estimated liver remnant represented only 13% of total liver volume, it was performed. During the first stage, we performed right portal branch ligation and in situ splitting, without right bile duct ligation. After the first stage, the patient did not develop biliary fistula, ascites or sepsis. The volume of segments 2 and 3 increased by 98% after eleven days, making possible subsequent resection of the tumor by a right trisectionectomy. The patient did not develop any complication, being discharged 9 days after the second stage of ALPPS. Postoperatively, the patient underwent chemotherapy, being disease-free at 13 months following operation.

Conclusion: This is the first patient presented in the literature who underwent ALPPS for resection of a primary hepatic lymphoma. This type of tumor could be managed by ALPPS, with low morbidity and mortality rates.

Abbreviations: ALPPS – Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy, PHL – primary hepatic lymphoma, PVE – portal vein embolization, PVL – portal vein ligation, FLR – future liver remnant

Key words: ALPPS, major liver resection, portal vein embolization, portal vein ligation, “two-stage” liver resection, primary hepatic lymphoma

INTRODUCTION

Primary hepatic lymphoma (PHL) is a non-Hodgkin lymphoma (NHL) that is typically confined to the liver, without evidence of lymph nodes, spleen,

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hematogenous bone marrow or other lymphoid structures involvement (1). The optimal therapy is not fully established, although most cases reported to date were treated with combined chemotherapy (2). However, over the last decade, several reports suggested that liver resection associated with postoperative chemotherapy appears to improve survival when compared to chemotherapy alone (3-7).

Thus, in PHL patients, the only contraindication for liver resection is technical impossibility to perform a complete tumor resection. This situation is similar to those encountered in patients with other malignant liver tumors (e.g., hepatocellular carcinoma, intrahepatic cholangiocarcinoma, colorectal liver metastases) without extrahepatic metastases. In such instances, the most frequent clinical scenario that precludes liver resection is insufficient volume of the remnant liver parenchyma (future liver remnant - FLR), which should represent at least 25% of total liver volume (TLV) in order to avoid postoperative liver failure. For these patients, several strategies were developed: liver resection after portal vein embolization (PVE) or ligation (PVL), "two-stage" liver resection (associated or not with PVL/PVE), resection after tumor shrinkage induced by preoperative chemotherapy, ultrasound-guided liver resections or combined ablation and resection (CARE).

Each of the above mentioned strategies presents some drawbacks: 1. in patients scheduled for liver resection after PVE/PVL, the increase of the FLR volume could be insufficient and, moreover, some patients could develop metastases in the FLR during the interval between PVL/PVE and the time of hepatectomy, making this procedure futile in up to 50% of cases; 2. patients scheduled for "two-stage" liver resection could develop new metastases in the FLR during the period between the two stages; 3. tumor shrinkage could be insufficient to afford subsequent complete tumor resection in more than 75% of patients; 4. ultrasound-guided liver resection is not operational for large tumors involving both right and left hemiliver; 5. the long-term results achieved by ablation (even associated with resection - CARE) are significantly poorer than those achieved by complete tumor resection. To overcome these drawbacks, a few years ago, a new surgical procedure was developed in order to achieve a more robust hypertrophy of the FLR, in a shorter period of time. This procedure, called "associating liver partition and portal vein ligation for staged hepatectomy - ALPPS", enables, at least theoretically, a higher increase of the FLR volume than PVE/PVL in a shorter period of time, decreasing the risk of development of new metastases in the FLR.

In the present manuscript, we report our experience with the first patient who underwent ALPPS at "Dan Setlacec" Center of General Surgery and Liver Transplantation from Fundeni Clinical Institute, Bucharest. We report short-term results in terms of FLR gaining and time of liver hypertrophy, as well as immediate and one-year postoperative course. Also, to the best of our knowledge, this is the first report of a PHL patient successfully addressed by ALPPS.

CASE REPORT

A 54 year-old woman with a BMI of 26.3 was initially seen for right upper quadrant tenderness. Of note, in 1998 she underwent total hysterectomy with bilateral anexectomy followed by radio-chemotherapy probably for carcinoma of the uterus (medical records unavailable). Her past medical history also included hydrocephalus (diagnosed in 2013), controlled by Acetazolamide.

Abdominal ultrasound revealed a large tumor involving right hemiliver, and a contrast-enhanced CT scan confirmed the presence of a tumor involving segments 4, 5, 6 and 8.

The volumetric evaluation of the liver showed that the TLV was 2139 cubic cm (cmc), and the volume of segments 2-3 was 294 cmc (13.7% of TLV - *fig. 1*). The radiologic features of the lesion were not suggestive of either hepatocellular carcinoma or intrahepatic cholangiocarcinoma, or of a benign liver tumor (hemangioma, adenoma or focal nodular hyperplasia).

The upper GI Endoscopy revealed grade I esophageal varices and the colonoscopy was normal.

Blood tests showed normal AST, ALT, Bilirubin,

Figure 1 - CT scan revealing a large liver tumor involving segments 4, 5, 6, 8 (volume of segments 2-3: 295 cmc, 13% of TLV)

AFP, CA 19-9 and CEA, and ruled out Hepatitis B or C infection. The only abnormal findings were dyslipidemia and slightly increased levels of CA 15-3 (64.7 U/ml).

Mammography was performed but it did not reveal any pathologic findings.

A multidisciplinary team decided to proceed with laparotomy with intraoperative biopsy and if frozen pathologic examination will reveal a malignant tumor to employ a strategy aiming at the resection of the tumor.

On February 19th 2015, the patient underwent laparotomy. Intraoperative findings (by palpation and ultrasonography) confirmed the presence of the tumor involving segments 4, 5, 6 and 8 with encasement of the middle hepatic vein and intraoperative flash-frozen biopsy established the diagnosis of NHL confined to the liver.

Because the initial complete resection of the tumor was not possible due to the insufficient remnant liver parenchyma (volume of segments 2 and 3 represented only 13% of TLV), an ALPPS approach was attempted.

The operation started with cholecystectomy, then, it was performed the mobilization of the right hemiliver with ligation and transection of the accessory veins draining into the inferior vena cava (IVC). The right hepatic vein was identified, but it was not transected.

Dissection of the hepato-duodenal ligament was carried out, identifying the right hepatic artery, right portal branch and right bile duct. The right portal branch was transected and the two stumps were sutured, while the right hepatic artery and right bile duct were left intact (*fig. 2a*). The parenchyma transection was performed following a plane located 1-2 cm to the right of the left intersectional plane (*fig. 2b*), splitting the liver in two parts (segments 2-3 – on the left side and the right hemiliver plus segment 4 – on the right side). In order to avoid the development of adhesions between the two parts of the liver, an inflated Foley catheter has been placed between them (along the transection plane - *fig. 2b*). Sampling of the lymph-nodes located paracaval and in the hepatic pedicle has also been performed.

The postoperative course was uneventful: the patient did not develop either biliary fistula, or ascites (the amount of abdominal drainage fluid was less than 200 ml daily). AST and ALT levels decreased from 255 U/l and 282 U/l, respectively (in postoperative day 1–POD 1) to 51 U/l and 77 U/l, respectively in the POD 5. The values of Bilirubin were within normal range every day.

In the POD 11, a CT scan with volumetric evaluation was performed, revealing the absence of postoperative fluid collections and the volume of segments 2-3 was

Figure 2 - a. The right portal branch transected and ligated. Right hepatic artery and right bile duct were not ligated. b. A Foley catheter placed on the transected surface of the liver

586 cmc (*fig. 3*). Thus, the FLR volume almost doubled after PVL and in situ splitting (from 294 cmc before operation, to 586 cmc after PVL and in-situ splitting), representing 27.3% of TLV. Thus, it was considered that the second stage could be safely performed, with low risk of postoperative liver failure.

Figure 3 - CT scan performed at 11 days after right portal branch ligation and in-situ splitting (volume of segments 2-3: 586 cmc, 27.3% of TLV)

On March 9th 2015 the patient underwent liver resection (right trisectionectomy). During laparotomy, the right hepatic artery and the right bile duct were ligated and divided, the right and middle hepatic veins were transected and the specimen was removed and sent for pathologic examination (*fig. 4*).

Postoperatively the patient presented transient ascites (1100 ml during the second postoperative day) treated with Manitol, achieving minimal peritoneal drainage by POD 6. AST and ALT levels became normal by the POD 5 and Bilirubin level was normal throughout.

The patient was discharged on POD 9 after the second operation, in good clinical condition, with normal liver enzymes.

The paraffin embedded examination of the tumor revealed a dense lymphoid infiltrate with small-sized cells that formed lymphoepithelial lesions on bile capillaries (*Fig 5*) and confirmed the diagnosis of NHL of the liver, without malignant cells in the harvested lymph nodes.

Immunohistochemical examination indicate that the lymphoma proliferation was positive for CD20 (*fig. 6*) (B-cell marker) and negative for CD3 (T-cell marker), Cyclin D1 (mantle-cell lymphoma marker), CD23 (follicular dendritic cell marker) and BCL6 (follicle centre cell marker). The diagnosis was low-grade small B-cell extranodal marginal zone lymphoma MALT (mucosa-associated lymphoid tissue) type.

Bone marrow trephine biopsy was without lymphoma infiltration.

The patient received 6 cycles of postoperative chemotherapy, with R-CHOP regimen (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone), starting in June 2015.

At the time of writing this manuscript, one year after liver resection, the patient is alive, in good clinical condition, without any evidence of recurrent disease.

DISCUSSION

To the best of our knowledge this is the first case reported in the literature of PHL resected by ALPPS procedure.

PHL is a rare pathologic condition, representing 0.016% of all cases of non-Hodgkin lymphomas (1). Until recently, the treatment of patients with PHL consisted of combined chemotherapy, but the prognosis was dismal in most cases, the median survival being 15.3 months after the diagnosis (according to a review of 72 cases) (8). However, due to the small number of cases, the optimal therapy is still unclear, but in the last years, liver

Figure 4 - The resected specimen

Figure 5 - Liver tumor – small-sized lymphoid proliferation (HE stain, ob. 20x)

Figure 6 - Liver tumor – small B-cell lymphoid proliferation, CD20 positive (IHC stain for CD20, ob. 20x)

resection associated with chemotherapy seems to be the treatment of choice in patients with PHL (3-7,9,10).

That was the reason why it was decided to resect this large liver tumor in the patient presented above, although initially complete resection was not possible due to the insufficient volume of the FLR.

Over the past two decades, the most used methods to enlarge the volume of FLR in patients with initially unresectable liver tumors were liver resection after PVE/PVL and “two-stage” liver resection (with or without PVE/PVL). The ratio of FLR hypertrophy is calculated with formula: $100 \times (\text{FLR Volume after PVE} - \text{FLR volume before PVE}) / \text{FLR volume before PVE}$ (11). By applying PVE or “two-stage” liver resection to increase the volume of FLR, the ratio of FLR hypertrophy ranged between 20% and 50% (12-17) within 2-8 weeks, enabling R0 liver resection in almost 66% of these patients (11,16,18-21). Few years ago, ALPPS has been launched as a novel surgical modality able to achieve a more robust hypertrophy of the FLR in a shorter period of time.

In a previous paper published by our center, the ratio of FLR hypertrophy achieved by PVL or “two-stage” liver resection associated with PVL was 43.8% at 6 weeks (16). In patient presented above, the ratio of FLR hypertrophy was 98% at 11 days, significantly higher than those reported with PVL. The higher hypertrophy ratio achieved by ALPPS procedure in the patient presented above is similar to those reported by other authors (22-24), who revealed a statistically significant increase in FLR volume after ALPPS than in patients undergoing PVE/PVL, allowing the performance of R0 resections in almost 100% of patients subjected to this new approach (25,26). Moreover, recent studies revealed that in patients who failed to achieve sufficient FLR hypertrophy after PVE, the performance of ALPPS was an effective strategy, able to induce a FLR gain which allowed subsequent R0 resection (26;27).

Moreover, this higher hypertrophy after ALPPS was achieved within 6-10 days (22-24), unlike the hypertrophy induced by PVE which was observed after 2-6 weeks. A multicentric analysis revealed an 11-fold faster hypertrophy after ALPPS than after PVE (28). As hypertrophy is achieved more rapidly after ALPPS, the complete resection of the tumor could be performed in a shorter period of time, which offers some benefits: 1. the risk of disease progression between the two stages of the operation decreases (25,29); 2. the patient recovers more rapidly, decreasing the length of hospital stay (25); 3. the postoperative chemotherapy could be delivered sooner than in patients undergoing “two-stage” operations (25).

However, the ALPPS procedure presents some drawbacks, the most important being those related to

the higher morbidity and mortality rates. Thus, major morbidity (Dindo-Clavien III or more) rates after ALPPS ranged between 27 and 41% in series presented until now (24,26,28,30,31). Moreover, the high mortality rates (up to 12.5% in most series) raise concerns about the indications, limits and surgical technique used for ALPPS (26,28). These factors were assessed in some recent papers and the authors recommended avoiding ALPPS in patients older than 60 years-old and in patients with hilar cholangiocarcinoma (28,32). Other experts also recommended avoiding ligation of the right bile duct during the first operation (30) and revealed that obesity, post-stage one biliary fistula and ascites or infected/bilious peritoneal fluid at stage two operation were significantly associated with major morbidity and mortality (26).

The favorable outcome of the patient presented above could be explained by several facts: the patient had normal BMI, was less than 60 year-old, did not receive chemotherapy in the few years leading to the surgical intervention, the tumor was a lymphoma (not a hilar cholangiocarcinoma) and the right bile duct was not ligated during the first stage of the surgical intervention. Furthermore, after the first stage, the patient did not develop biliary fistula or ascites and, at the time of the second operation, infected or bilious peritoneal fluid was not present. Thus, the patient did not present any of the poor prognostic factors reported in the literature, revealing that an accurate indication and an elaborate surgical technique are able to avoid the increased morbidity and mortality rates in patients undergoing ALPPS procedure.

Moreover, the survival of this patient, which is alive and disease-free 1 year after hepatectomy, seems to justify the efforts to resect the PHL. We consider that the disease-free survival of the patient at one year following ALPPS represents a promising result, taking into account the median survival of only 15.3 months reported in a review of the literature which analyzed mainly patients treated with chemotherapy alone (10). In 2010, Yang X. W. presented a series of 9 patients undergoing liver resection and postoperative chemotherapy for PHL and reported a median survival of 23 months, which seems to be superior to those achieved by chemotherapy alone (6). Moreover, in a more recent series, of 35 patients undergoing liver resection and chemotherapy for PHL, the median survival of patients with B-cell PHL (31.7 months) was statistically significant higher (p value < 0.05) than those achieved in patients presenting T-cell PHL (22.9 months) (33).

In conclusion, although the optimal treatment of primary hepatic lymphoma is still unclear, liver resec-

tion associated with chemotherapy seems to prolong survival of these patients. ALPPS could represent an attractive surgical strategy aiming conversion to resectability of initially unresectable liver tumors, when the indication is adequate and surgical technique is well elaborate. PHL seems to be a type of tumor which can benefit from ALPPS procedure, with low postoperative risks. The hypertrophy of the future liver remnant achieved by ALPPS is higher than those reported after portal vein embolization/ligation and it is accomplished in a shorter period. Thus, ALPPS enables resection of initially unresectable liver tumors in most patients with initially insufficient FLR, decreasing the risk of tumor progression until the second operation.

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