Ante situm liver resection with inferior vena cava replacement under hypothermic cardiopulmonary bypass for hepatoblastoma: Report of a case and review of the literature

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ABSTRACT

INTRODUCTION: Hepatoblastoma with tumour thrombi extending into inferior-vena-cava and right atrium are often unresectable with an extremely poor prognosis. The surgical approach is technically challenging and might require major liver resection with vascular reconstruction and extracorporeal circulation. However, which is the best surgical technique is yet unclear.

PRESENTATION OF CASE: A 11-months-old boy was referred for a right hepatic lobe mass (90 × 78 mm) suspicious of hepatoblastoma with tumoral thrombi extending into the inferior-vena-cava and the right atrium, bilateral lung lesions and serum alpha-fetoprotein level of 50,795 IU/mL. After 8 months of chemotherapy (SIOPEL 2004-high-risk-Protocol), the lung lesions were no longer clearly visible and the hepatoblastoma size decreased to 61 × 64 mm. Thus, ante situm liver resection was planned: after hepatic parenchymal transection, hypothermic cardiopulmonary bypass was started and en bloc resection of the extended-right hepatic lobe, the retro/suprahepatic cava and the tumoral thrombi was performed with concomitant cold perfusion of the remnant graft. The inferior-vena-cava was replaced with an aortic graft from a blood-group compatible cadaveric donor. The post-operative course was uneventful and after 8 months of follow-up the child has normal liver function and an alpha-fetoprotein level and is free of disease recurrence with patent vascular graft.

CONCLUSIONS: We report for the first time a case of ante situm liver resection and inferior-vena-cava replacement associated with hypothermic cardiopulmonary bypass in a child with hepatoblastoma. Herein, we extensively review the literature for hepatoblastoma with thrommal thrombi and we describe the technical aspects of ante situm approach, which is a realistic option in otherwise unresectable hepatoblastoma.

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Abbreviations: HLB, hepatoblastoma; IVC, inferior vena cava; FAP, familial adenomatous polyposis; LT, liver transplantation; PV, portal vein; TVE, total hepatic vascular exclusion; UVC, upper vena cava; PRE-TEXT, pre treatment extent of disease; POST-TEXT, post treatment extent of disease; SIOPEL, Société Internationale d’Oncologie Pédiatrique-Éphémital Liver Tumor Study Group.

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1. Introduction

Hepatoblastoma (HBL) is the most common paediatric liver tumour and it occurs usually in the first 3 years of life. The incidence of HBL has increased in the recent years up to 1.5 cases per million, and it is frequently associated with low birth weight or genetic anomalies. The management of HBL has impressively improved due to combined neo-adjuvant chemotherapy and liver resection or liver transplantation (LT), increasing the overall 5-years survival rate up to 75% [1]. The risk stratification with the pre-treatment extent of disease (PRE-TEXT) system, the worldwide multicentre trials experience and the multidisciplinary management, improved HBL prognosis and surgical resectability [2]. However, HBL with tumour thrombi extended into the inferior vena cava (IVC), with or without the involvement of the right atrium, may result challenging to define the best surgical technique.

Different surgical procedures, mainly reported in adults, have been proposed for liver tumour with IVC involvement, including total hepatic vascular exclusion (TVE) [3]. These techniques are effective to control haemorrhage and air embolism during liver resection, but may cause severe hepatic ischaemia/reperfusion injury, hemodynamic instability and potential renal injury. Recently, liver resection under hypothermic liver perfusion with cytoprotective solution (including in situ, ex situ or ante situm techniques) has been proposed for preventing ischemic liver injury [4]. Yet, no experience of ante situm liver perfusion associated with hypothermic cardiopulmonary bypass has been reported in children.

Herein we report a successful case of ante situ liver resection and IVC replacement under hypothermic cardiopulmonary bypass (CPB), performed in a 21-months-old male with HBL and tumour thrombi into the IVC and right atrium.

The current case has been reported in line with the SCARE criteria [5].

2. Case report

The patient was a 11-months old child referred for right upper quadrant abdominal mass. He was born on term (birth weight of 2.470kg) and had a familial history of adenomatous polyposis (FAP). At the time of admission, the patient was asymptomatic with normal vital signs, but physical examination revealed hepatomegaly, abdominal bloating and umbilical hernia. The ultrasonography (US) showed a large hepatic mass (10 cm in diameter) in the right liver. Serum alpha-fetoprotein (AFP) level was 50,795 IU/mL. Liver function, coagulation, serum B-human chorionic gonadotropin, blood cell count, thyroid function were within normal limits, except for the evidence of thrombocytosis (805,000/UL). Computed tomography (CT) showed a mass of the right hepatic lobe, 90 x 78 mm in size extending in segment IV, with dyshomogeneity and calcifications. The tumour displaced posteriorly the right kidney, dislocated the aorta and the IVC to the left side, stretching the celiac trunk and the superior mesenteric artery (Fig. 1). Tumoral thrombi was present, extending from the right hepatic vein into the IVC up to the right atrium. Bilateral lung lesions, suspicious for HBL metastases, were found as well. Heart involvement was confirmed by echocardiography, which detected a 2.6 cm echoic mass through the tricuspid valve.

A PRE-TEXT III staging (P0, V3, M1) with lung and atrium-cava metastasis at the outset was defined. The child underwent neoadjuvant chemotherapy (SIOPEL 2004 high risk protocol; cycles A1-3 and cycle B) for 8 months: 3 cycles with cisplatin (70 mg/m², 9 doses administered) and doxorubicin (30 mg/m², 6 doses); 4 cycles with carboplatin (6 mg/Kg, 4 doses) and doxorubicin (0.83 mg/Kg, 10 doses); and 2 cycles with carboplatin (25 mg/Kg, 2 doses), vincristine (0.05 mg/Kg, 5 doses) and 5-fluorouracil (33 mg/Kg, 6 doses). During the treatment, the child presented transient severe thrombocytopenia and one episode of sepsis successfully treated with antibiotics. After neo-adiuvant therapy AFP decreased to 879 IU/mL. CT scan showed size reduction of the HBL (61 x 64 mm), still involving the IVC as the right and middle hepatic vein. A left accessory hepatic artery from the left gastric artery and a replaced right hepatic artery arising from the superior mesenteric artery were documented; lung lesions were no longer clearly visible. Cavography documented retroheaptic IVC infiltration by HBL (Fig. 2). After multidisciplinary team meeting (involving surgeons, oncologist, anaesthesiologist and radiologist), the small patient was proposed for an extended right liver resection, with IVC and intracardiac thrombus removal, which was performed by a senior liver transplantation and hepato-biliary-pancreatic surgeon.

2.1. Surgical procedure

The patient was placed in supine position and the abdomen was explored through a bilateral sub-costal incision with xyphoid extension. There was no evidence of ascites or peritoneal metastasis and intraoperative US documented that the tumour did not involve the left lateral segment of the liver. The Arantius’ ligament was dissected and the left hepatic vein was looped. After cholecystectomy, the common bile duct, the right hepatic artery and the anterior and posterior branches of the right portal vein (PV) were ligated and divided. The left PV and the left hepatic arteries were identified and looped. The Rex recess was then exposed and vessels for segment IV were divided. Parenchymal transection, along the line of the falciform ligament, was performed via an anterior approach, using the hanging manoeuvre with “no touch approach” of the tumour. Biliary and vascular structures were divided between clips or tie. Pringle manoeuvre was not used. A vessel loop around the IVC above the renal veins was then placed.

The xiphoid incision was extended up to the jugulum with a median sternotomy and the pericardial sac was opened. After systemic heparinization, the ascending aorta, the upper vena cava (UCV) and the infra-renal IVC were cannulated and clamped, and the extracorporeal circulation with CPB was started. Body temperature was reduced to 28 °C, in order to protect the organs. The diaphragm was incised vertically down toward the suprahepatic IVC and the diaphragmatic veins were divided. After clamping the left hepatic arteries and the PV, the left PV was cannulated though the right PV stump. The left hepatic vein was divided and ante situm hypothermic liver perfusion with Celsior solution (4 °C) was started. The liver was further cooled with ice on his surface. After division of the right triangular ligament, an en bloc resection of the extended-right hepatic lobe (segments I + IV-VIII), of the retro- and supra-hepatic IVC and of the neoplastic thrombus (extending from the right hepatic vein to the right atrium) was performed (Fig. 3). The IVC was reconstructed with a fresh aortic graft from cadaveric donor with identical blood group. The aortic conduit was end-to-end anastomosed with the right atrium (through the diaphragmatic ostium) and inferiorly with the supra-renal IVC by 5/0 prolene continuous running sutures. The neo-IVC was opened immediately below the diaphragmatic ostium and end-to-side triangular anastomosis was performed between the left hepatic vein and the neo-IVC by 6/0 prolene. After 40 min of hypothermic liver perfusion, the portal flush was interrupted. UVC, IVC, aorta, left hepatic arteries and PV were de-clamped, and the left lateral segment was reperfused. The patient was gradually warmed and, once hemodynamic stability and good haemostasis were confirmed, the CPB was weaned off, after a total time of 71 min. Roux-and-Y end-to-end hepaticojenumostomy with 6/0 PDS was performed for biliary reconstruction. Before thoraco-abdominal closure, Doppler-US established a good flow through the neo-IVC, left hepatic vein, left hepatic arteries, and PV. The total operation time was 8 h and
10 min, with a blood loss of 200 ml (video of the surgical technique can be found in supplementary materials).

The resected liver specimen weighted 210 g. The tumour measured 8 × 9 cm. Histological diagnosis was HBL, mixed epithelial and mesenchymal type, with teratoid features, invading the hepatic venous system extensively. The surgical margins were clear from tumour.

2.2. Post-operative outcome

The child had an uneventful post-operative course and was discharged after 23 days from surgery.

After 4 months, a staging CT scan showed absence of disease recurrence and good liver perfusion, with patent aortic graft (Fig. 4). After 12 months of follow-up the child is in good clinical condition with normal liver function test and an AFP level of 1.1 UI/mL.

3. Discussion

HBL is the most common primary paediatric liver tumour, with greater frequency among males. The main symptoms include discomfort due to the abdominal mass and loss of appetite, associated with generalized fatigue secondary to anaemia. Most HBLs are sporadic, but some are associated with genetic abnormalities and malformations, such as trisomy 18, Beckwith-Wiedemann syndrome, or FAP [1]. HBL should be suspected in patients aging between 6 months and 3 years old in the presence of an hepatic tumour with thrombocytosis and high AFP levels, which were all present in our case. Histologically, HBL has been classified in the epithelial type, which is the most common and presents with a combination of mixed embryonal and fetal patterns, and in the mesenchymal type, which occurs with or without teratoid features. Yet, most HBLs are extremely heterogenous, often with mixed
histological components, and only rarely composed of a single histological type. Mesenchymal elements have been associated with an improved prognosis in patients with advanced disease, as it was in our case [2].

The PRE-TEXT system allows to stage and stratify the risk of HBL and to define its prognosis and surgical resectability. Although 60% of tumours are unresectable at presentation, HBL is highly chemosensitive and up to 85% of cases become operable after neoadjuvant chemotherapy [2].

The best chemotherapy for advanced tumours is still controversial. The platinum-based chemotherapeutic regimens have been essential in improving patient survival in advanced HBL. The Children's Oncology Group (COG) recommends cisplatin, 5-fluorouracil and vincristine, associated with doxorubicin for intermediate and high-risk patients, while the Société Internationale d’Oncologie Pédiatrique-Epithelial Liver Tumor Study Group (SIOPEL) recommends in very high-risk patients cisplatin intensification therapy (SIOPEL-4 protocol) [2].

In the current case the SIOPEL 4 protocol was used accordingly with presence of metastatic disease and major vascular invasion. Since tumour remained unresectable at the first CT re-evaluation with high AFP levels, he received additional preoperative chemotherapy before surgery was attempted (data not shown).

Complete surgical removal of HBL, by resection or LT, remains the only treatment achieving long-term survival. LT plays a key role in the management of children with large and multifocal HBL, but equivalent long-term disease-free survival have been recently achieved with large non-anatomic or extended liver resection, provided that complete macro- and micro-scopic tumour resection can be achieved [6].

Although it must be carefully considered on a case-by-case basis, multidisciplinary post treatment extent of disease (POST-TEXT) tumour evaluation and intraoperative liver inspection are essential to define the best therapeutic management. In this sense, prompt referral to a center with expertise in both paediatric LT and extreme resection must be considered the gold standard in care giving. POST-TEXT tumours that spare at least 1 branch of the portal vein and 1 hepatic vein should always be evaluated for liver resection. When venous obstruction, encasement, and/or invasion of the main portal vein or bifurcation of the IVC or all 3 hepatic veins are present, the tumour is classified unresectable and intended to transplantation [2].

In this case we opted for a major liver resection with IVC reconstruction because of evidence of lung metastasis and presence of left lateral liver free of disease with adequate remnant liver volume. Hepatic resection avoided exposing the young boy to long-term immunosuppression.

Tumour thrombi in the hepatic veins and IVC with an extension up to the atrium are associated with high risk of pulmonary embolism, occlusion of the tricuspid valve (ball valve syndrome),

Fig. 3. Technical aspects of ante situm liver resection and inferior vena cava replacement. Intraoperative view of A) hepatic hilum dissection; B) parenchymal transection, on the line of the falciform ligament via anterior approach; C) ante situm hypothermic liver perfusion with Celsior solution (4°C) through the right portal vein stump and inferior vena cava replacement with donor aortic conduit (note the diaphragmatic ostium resected and reconstructed); D) final view of en-bloc resection of the extended-right hepatic lobe (segments I+IV-VIII), the inferior vena cava with tumoral thrombi and the diaphragmatic ostium.
congestive heart failure and spread of systemic metastasis and are mainly reported in adults with hepatocellular carcinoma [3].

Despite surgical treatment seems to remain the only effective therapeutic option, there is no established management for such cases. In 1966, Heaney et al. firstly proposed the TVE of the liver [7]. TVE is effective in controlling haemorrhage and air embolism, but causes severe hemodynamic disturbances characterized by >30% decrease in mean arterial pressure, >50% decrease of cardiac index and severe ischemic liver damage, in particular in small remnant liver after neoadjuvant chemotherapy [3]. Even if it is not mandatory, it is advisable to use TVE in combination with CPB in order to reduce hemodynamic instability and potential renal injury, in particular when pronged TVE is required.

In 1981, Ein et al. described the first successfully use of CPB associated with hypothermic cardiocirculatory arrest in 6 children with right atrial tumoral thrombi [8]. However, the procedures were associated with high post-operative haemorrhage and microscopic residual tumour (R1). Later, further reports of major HBL resections using the CPB have been reported, as summarized in Table 1. Many cases have been associated with major complications such as post-operative dead for pulmonary embolism (possibly related to tumoral thrombi spreading during liver mobilization) [9]; ischemic cholangiopathy requiring subsequent LT [10]; residual tumoral thrombi in major vessels [6].

To reduce ischemic damage related to TVE and cellular metabolism during this phase, the concept of hypothermic preservation, by liver perfusion with cytoprotective solutions combined with cooling of the organ's surface, has been investigated. In 1974, Forner et al. described the first in situ hypothermic liver perfusion during major liver resection, where hypothermia was induced by liver perfusion via the arterial and portal system with cold Ringer’s solution (4 °C) [11]. However, in case of tumours located on the posterior side of the liver and invading the IVC, in situ hypothermic liver preservation may not be sufficient to expose the retro-hepatic vena cava. Consequently, in 1990 Pichlmayr et al. proposed the ex situ liver perfusion [12], where the liver is completely removed from the patient, cooled with ice and perfused with cold solution on the backtable; after the bench surgery the remnant liver is reimplanted orthotopically. Later, in 1991 Hannoun et al. [13] introduced the ante situm liver resection characterized by no hepatoduodenal ligament division, cold liver perfusion, TVE and division of the supra-hepatic IVC, which allows the rotation of the liver around the coronary axis with optimal exposure of the hepatic veins confluence and the retro-hepatic IVC. Belghiti et al. described the modified ante situm technique in which the IVC is cut above and below the liver, permitting a better mobilization of the liver [14]. A recent review of hypothermic ante situm resection in tumour of the hepatocaval confluence suggests that this approach is easier and safer than the ex situ technique, with an acceptable morbidity and mortality rate [4].

To the best of our knowledge, the current report is the first case of ante situm liver resection and IVC replacement with hypothermic CPB for HBL in a young child. Since the tumour was involving the extended right lobe of the liver with the retro-hepatic IVC and the right atrium, the CPB was needed. Anterior approach to the liver was adopted performing parenchymal transection with “no touch technique” of the lesion, to avoid tumoral embolization. Moreover, to reduce the risk of bleeding during this phase, liver resection was completed before eparinization and CPB, differing from previous reports. The modified ante situm technique permitted to expose optimally the retro-hepatic cava by cutting the IVC above and below the liver, to mobilize the liver anteriorly and to reduce the ischemia liver injury of the remnant segments by PV perfusion. Furthermore, we didn’t divide the liver hilum, avoiding the risk of hepatic artery thrombosis.

So far, the largest series of the ante situm liver resection was reported by Raab et al.: out of 24, one adult patient had HBL [15]. Authors adopted a normothermic vein bypass and IVC reconstruction was performed with autologous saphenous; however, details regarding the outcome of the HBL patient are not available.

In the current report a simple trombectomy was not feasible since the tumoral thrombi infiltrated the IVC wall. Therefore, retro-hepatic IVC resection and interposition of graft were needed to achieve R0 resection. The options to reconstruct the IVC include pri-
Table 1

| Literature report | Year | Cases | Age (months) | Gender | Type of vascular infiltration | Type of liver resection | Adjuvant chemotherapy | Metastatic disease* | IVC reconstruction | CPB (type, min) | Outcome |
|-------------------|------|-------|--------------|--------|-------------------------------|-------------------------|----------------------|-------------------|------------------|---------------|---------|
| Ein et al. [9]     | 1981 | 1     | NA           |        | None                          | None                    | None                 | None              | None             | Hypothermic   | Died/2 Alive |
| Meissner et al. [10]| 2001 | 1     | 36M          | RA     | None                          | RA                      | VCR, CIS, SPU, VCDX  | None              | Right hepatico-embolotomy | Hypothermic   | Alive, NED  |
| Lautz et al. [8]   | 1991 | 1     | NA           | RA     | None                          | RA                      | VCR, CIS, SPU, VCDX  | None              | Right hepatico-embolotomy | Hypothermic   | Alive, NED  |
| Fuchs et al. [6]   | 2016 | 2     | NA           |        | None                          | RA                      | None                 | None              | Platinum-based | Hypothermic   | Alive, NED  |
| Current case       | 2016 | 2     | 117M         |        | None                          | DVC-RA                  | DVC-RA               | None              | None             | Hypothermic   | Alive, NED  |

Abbreviations: DVC-RA, Carbo-induced chemotherapy; CPB, cardiopulmonary bypass; DVO, distal vascular occlusion; CRS, conventional resection; VCDX, vascular carcinoma; IVC, inferior vena cava; NED, no evidence of disease; NA, non-applicable.

In conclusion, although the significance of our data is limited by the case-report nature of our surgical practice, the current case suggests that ante situm liver resection is feasible in children with liver tumours considered unresectable by conventional surgery or when LT is contraindicated or considered as a second-line treatment. The use of hypothermic CPB is safe and allows expanding surgical indications when prolonged TVE with complex vessel reconstruction are needed. Patient selection, preoperative evaluation of the liver function and anatomy as well as intraoperative assessment are essential to achieve good outcome. Our findings justify further investigations to identify the optimal surgical management for children with large and centrally located liver tumours.

Conflicts of interest

No conflicts of interest

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Ethical approval

Not applicable

Consent declaration

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

- Roberta Angelico – Data collection, analysis, review of the literature and wrote manuscript
- Annalisa Passariello – Oncological management, intellectual content, review of the literature
- Pilotone Michele – Performed the cardiothoracic surgery, intellectual content
- Cozzolino Tommaso – Oncological management, data collection, review of the literature
- Piazza Marco – Oncological management, analysis and interpretation, intellectual content
- Miraglia Roberto – Data collection, analysis and interpretation
- D’Angelo Paolo – Oncological management, analysis and interpretation
- Capasso Mariella – Analysis and interpretation, intellectual content
- Saffioti Maria Cristina – Data collection, analysis and interpretation
- Alberti Daniele – Planning of surgical strategy, intellectual content
- Spada Marco – Performed the abdominal surgery, draft the work, intellectual content, senior author
Guarantor
Marco Spada.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijscr.2017.06.008.

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