Transabdominal Intrapericardial Approach in Liver Transplantation for Unresectable Primary Hepatic Functioning Paraganglioma With Invasion Into Hepatic Veins and Suprahepatic Vena Cava: A Surgical and Anesthesia Management Challenge

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ABSTRACT

Primary hepatic functional paraganglioma is a rare form of extra-adrenal catecholamine-secreting tumor. Definitive treatment of functioning paraganglioma is challenging because of the critical location of the tumor frequently in close proximity to vital structures and risk of excessive catecholamine release during operative manipulation. We report the multidisciplinary management approach for a case of unresectable primary hepatic functional paraganglioma with invasion into the hepatic veins and suprahepatic vena cava.

To our knowledge, this is the first report showing that orthotopic liver transplantation is curative for patients with unresectable primary hepatic paraganglioma. For locally advanced unresectable hepatic paraganglioma that involves the intrapericardial vena cava, a meticulous pre- and intraoperative medical management and transabdominal intrapericardial vascular control of the suprahepatic vena cava during orthotopic liver transplantation allows for complete extirpation of the tumor and achieves optimal outcome.

PHEOCHROMOCYTOMAS and paragangliomas are rare catecholamine-secreting neuroendocrine tumors that come from the same type of chromaffin cells but differ in location of origin [1–3]. While pheochromocytomas form in the adrenal medulla, paragangliomas arise from extra-adrenal chromaffin cells. Most pheochromocytomas and paragangliomas are benign. However, the incidence of malignancy is higher for paragangliomas (15%-35%) compared with pheochromocytomas (10%) [1]. The clinical presentation may include symptoms of catecholamine excess (functioning tumor) or be completely asymptomatic (nonfunctioning tumor). For patients with functioning paragangliomas, the symptoms include paroxysmal hypertension, headache, palpitation, and sweating.

Paragangliomas are typically located along the paraaortic sympathetic chain from the skull base to the pelvic floor. Although the liver is the second most common site of metastasis (after bone) from malignant pheochromocytomas or paragangliomas, primary hepatic paragangliomas are extremely rare [4–11]. Surgical debulking is rarely curative for malignant paraganglioma and is only considered as a palliative therapy. As such, preoperative surgical planning with curative intent should always aim for a surgical resection of the tumor including all microscopically detectable disease (R0 resection). Treatment of functioning paragangliomas is challenging because of the critical location of the tumor frequently in close proximity to vital

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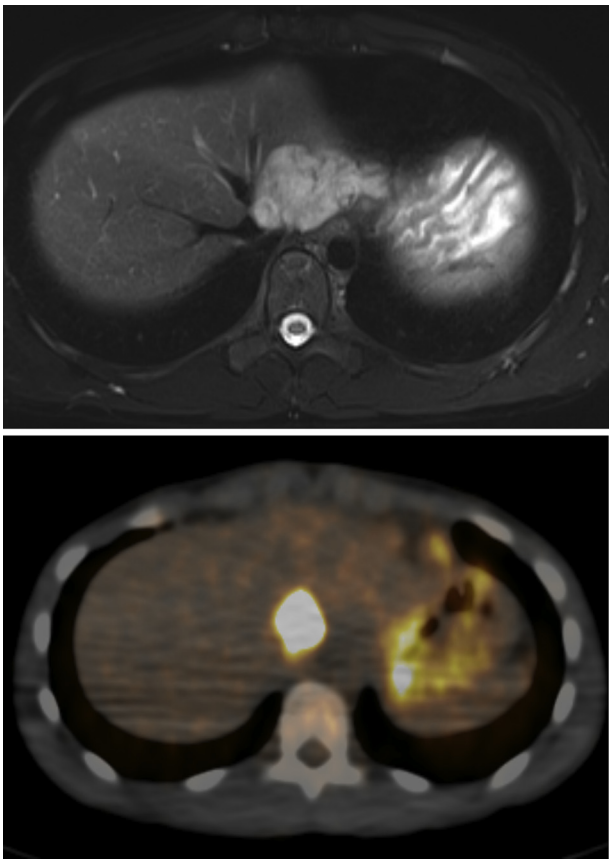

Fig 1. Magnetic resonance imaging and ^{18}F fludeoxyglucose positron emission tomography-computed tomography findings demonstrating invasion into the inferior vena cava.

structures and risk of excessive catecholamine release during operative manipulation [3]. We report the multidisciplinary management approach for a case of unresectable primary hepatic functional paraganglioma with invasion into the hepatic veins and suprahepatic vena cava. To our knowledge, this is the first report showing clinical applicability and safety of orthotopic liver transplantation (OLT) for this extremely rare disease. Furthermore, we described the importance of meticulous peri- and intraoperative medical and surgical planning and management to achieve optimal patient outcome.

CASE REPORT

Clinical Presentation and Diagnostic Tests

A 16-year-old man, 177 cm in height and 66 kg in weight, presented with new onset right eye pain with blurriness and headache secondary to hypertensive crisis (196/135 mm Hg). Examination showed bilateral papilledema without retinal hemorrhage and a grade 1 systolic ejection murmur in the upper sternal border with radiation to the axillae bilaterally. The remainder of the physical examination was normal. A complete blood count revealed an elevated hematocrit of 51 mg/dL. Other initial laboratory tests including a complete metabolic panel, thyroid function, and

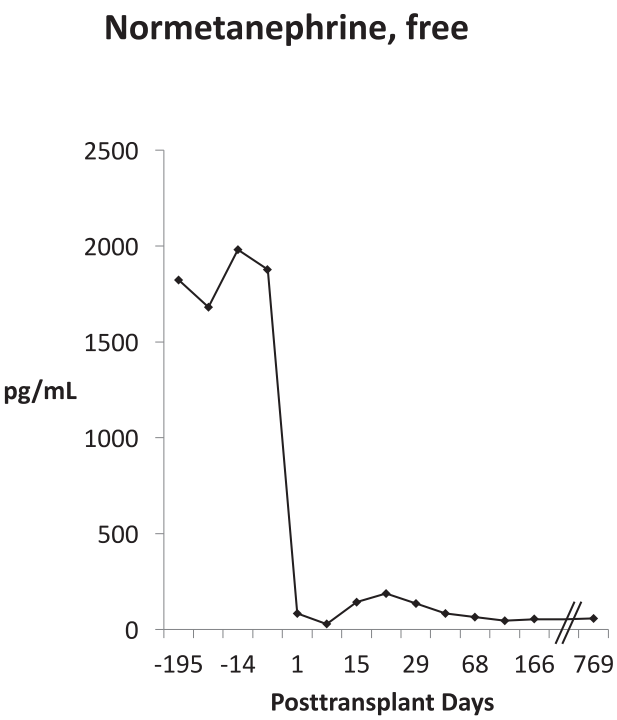

Fig 2. Pre- and posttransplant serum free normetanephrine levels.

urinalysis were within normal limits. Brain computed tomography (CT) scan and renal ultrasound were normal, and an echocardiogram demonstrated severe left ventricular hypertrophy.

A CT angiogram of the abdomen and pelvis demonstrated irregularly shaped and poorly circumscribed tumor in the dome of the liver at the confluence of middle and left hepatic veins, with the longest diameter being 6.7 cm. There was no evidence of renal artery stenosis, and the adrenal glands were normal. I-123 metaiodobenzylguanidine scan demonstrated normal uptake in the adrenal glands. Magnetic resonance imaging showed a well-defined 3.8 × 6.4 × 4.1 cm tumor, which was T2 hyperintense and T1 hypointense, with significant restricted diffusion and avidly enhancing lesion in segment 4 of the left lobe of the liver that extended into the suprahepatic vena cava (Fig 1). No magnetic resonance imaging finding suggested presence of any adrenal, extra-adrenal or paraspinal tumor. A whole body ^{18}F fludeoxyglucose positron emission tomography CT scan demonstrated focal avid increased uptake in the liver lesion at segment 4 (Fig 1) without any other areas (ie, adrenal glands or paraspinal soft tissues) of increased uptake, excluding other primary paraganglioma and metastatic disease.

Urine and plasma catecholamine levels revealed elevated urine metanephrine (3652 μg/g Cr, RR 156–442 μg/g Cr), urine normetanephrine (3753 μg/g Cr, RR: 91–365 μg/g Cr), and plasma free normetanephrine (1823 pg/mL, RR: < 148 pg/mL). In keeping with imaging and laboratory findings, including the plasma free normetanephrine of greater than 4 times the upper limit of normal, a diagnosis of the paraganglioma was made [12].

Preoperative Treatment Planning and Management

A multidisciplinary team involving hepatobiliary-transplant surgery, hepatology, oncology, anesthesiology, and radiology services

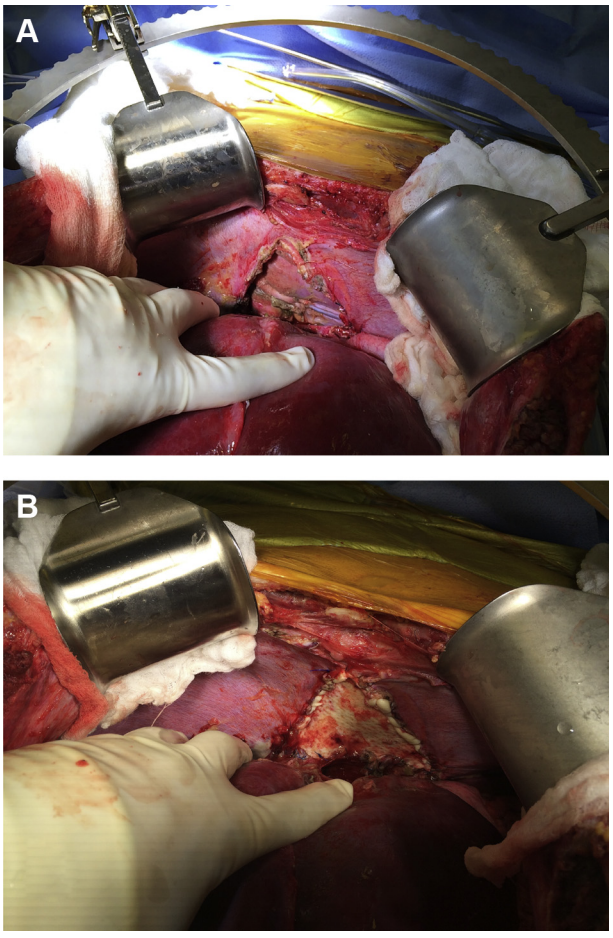

Fig 3. **(A)** Intraoperative photo showing transabdominal intrapericardial vascular control of inferior vena cava and hepatic venous outflow anastomosis during orthotopic liver transplantation. **(B)** Intraoperative photo showing reconstruction of the diaphragmatic defect with a biological tissue matrix.

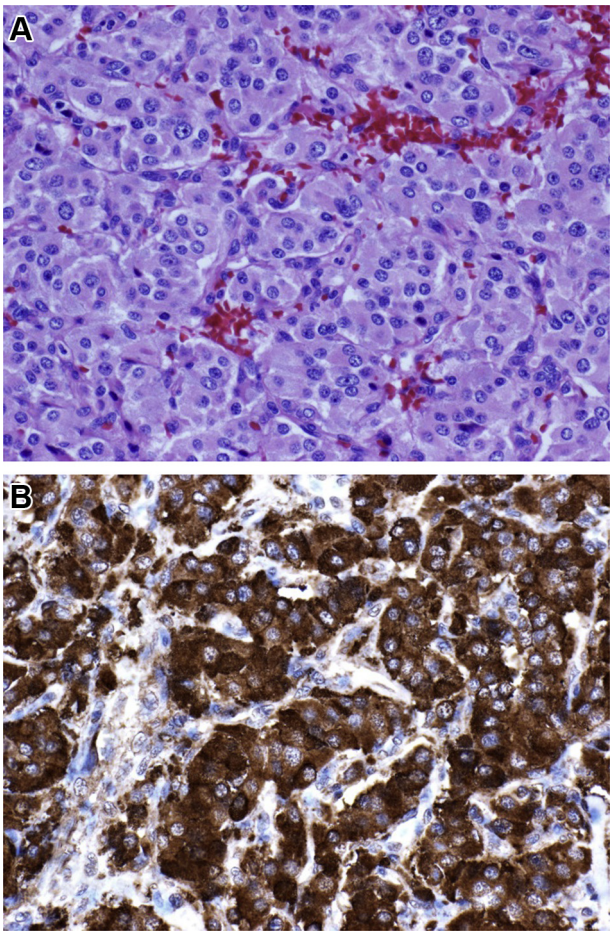

Fig 4. Histologic tumor staining for H&E **(A)** and chromogranin **(B)**.

developed a treatment plan that incorporated the management of systemic hypertension and neoadjuvant therapy aimed to reduce the tumor burden followed by surgical treatment. The neoadjuvant therapy included 2 treatments with transcatheter arterial embolization of the hepatic tumor and 2 cycles of systemic chemotherapy (vincristine, cyclophosphamide, dacarbazine). However, in the absence of a favorable response of the tumor from the neoadjuvant therapies and large size of the hepatic tumor that extended into the intrapericardial inferior vena cava, the team deemed the tumor not amenable to hepatic resection. As such, OLT was planned.

Anesthesia Peri- and Intraoperative Hemodynamic Management

Preoperative antihypertensive therapy included alpha-adrenergic blockade (phenoxybenzamine, 80 mg orally daily) and beta-adrenergic blockade (atenolol, 25 mg orally daily). On the day of OLT, phenoxybenzamine and atenolol were held and IV phentolamine, an intravenous alpha-adrenergic blocking agent with a short half-life ($t½ = 19$ minutes), was initiated. Intraoperative monitoring included electrocardiogram, pulse oximetry, noninvasive and invasive arterial blood pressure, central venous pressure, and 2-site (cerebral and somatic) near-infrared spectroscopy (Somanetics INVOS, Troy, Mich, United States) [13]. Anesthesia was induced with intravenous midazolam, fentanyl, and sevoflurane and maintained with fentanyl, isoflurane, and cisatracurium.

The patient experienced several periods of labile hemodynamics during OLT. During total native hepatectomy and manipulation of the tumor, swings in systolic blood pressure ranged from 36 to 252 mm Hg. Short-acting vasoactive drugs including norepinephrine, epinephrine, and sodium nitroprusside were titrated to attempt to dampen swings in the systemic blood pressure. After total excision of the hepatic paraganglioma, the patient developed profound persistent vasodilation despite discontinuation of intravenous phentolamine and required short-term replacement treatment with norepinephrine. During the posttransplantation period, the hemodynamic monitoring and management continued with transition to oral amlodipine and atenolol. Plasma normetanephrine levels dropped to the normal range immediately following the liver transplantation and remained within a normal range (Fig 2).

Surgical Technique

The OLT was performed with adjunct therapy of a total peripheral and mesenteric venovenous bypass. During total native

Table 1. Primary Hepatic Paraganglioma

First Author	Year	Functioning tumor	Symptoms	Size, cm	Sex	Age, y	Treatment	Follow-up	Recurrence
Jaeck [6]	1995	Yes	Hypertension, nocturnal sweating	5	Male	24	Segmentectomy 8	3 years	No
Reif [9]	1996	Yes	Palpitations, sweating, headaches, and hypertension	4.5	Female	42	Right hemihepatectomy	Not available	Not available
Rimmelin [10]	1996	Yes	Hypertension, nocturnal sweating	5	Male	24	Liver resection	3 years	No
Corti [5]	2002	No	None	8	Male	46	Right hemihepatectomy	9 years	No
Chang [4]	2006	Yes	Hypertension	6	Male	37	Right hemihepatectomy	5 years	No
Khan [7]	2011	No	Generalized body aches, headaches, and fever	20	Male	24	Extended right hepatectomy	3 years	No
Koh [8]	2013	No	Pain	18	Female	48	Liver resection	Not available	Not available
You [11]	2015	Yes	Hypertension	4	Female	47	Left lateral sectionectomy	4 years	Yes
Present report	2018	Yes	Hypertension, headaches, right eye pain, and blurriness	7.4	Male	16	Liver transplantation	32 months	No

hepatectomy, intraoperative findings confirmed a large centrally located hepatic tumor involving the right, middle, and left hepatic veins, as well as a tumor extension into the intrapericardial suprahepatic vena cava. Following porta hepatis dissection and isolation of the native hepatic artery, portal vein, and bile duct, a transabdominal intrapericardial vascular approach to obtain the suprahepatic vena cava vascular control was performed. The diaphragm was incised at approximately 10 cm in a vertical direction above the vena cava with electrocautery. Through this incision, the intrapericardial portion of the suprahepatic vena cava cephalad to the tumor was carefully isolated and encircled with a cotton tape [14]. Following complete dissection of the porta hepatis and isolation of the native hepatic artery, portal vein, and bile duct, vascular clamps were applied on the infrahepatic and intrapericardial suprahepatic vena cava. A total hepatectomy was performed with en bloc resection of the entire tumor, central diaphragm, a segment of the intrapericardial vena cava, and a portion of the pericardium.

The surgical procedure for deceased donor whole-organ OLT was performed in a standard manner with replacement of the recipient inferior vena cava. Aside from the need to perform the suprahepatic vena cava anastomosis for the hepatic allograft venous outflow in the pericardial space (Fig 3A), the rest of the surgical technique of allograft implantation was performed in the usual standard manner [15]. A staged choledochocholedochostomy was performed 2 days after OLT. In addition, the diaphragmatic defect was reconstructed using a biological tissue matrix (Alloderm Regenerative Tissue Matrix, Allergan, Dublin, Ireland), and a pericardial window was created to prevent accumulation of reactive pericardial effusion and cardiac tamponade after closure of the pericardium and diaphragmatic defect (Fig 3B) [14]. An anterior thoracotomy at the fifth interspace was performed, and a portion of the pericardium was resected, creating a small communication between the pericardial sac and the left pleural space to allow adequate drainage. Chest tubes were placed and subsequently removed on the 15th postoperative day. The patient did not develop any sign or symptom of pericardial tamponade based on hemodynamic monitoring and surveillance transthoracic cardiac echocardiography. At 32 months post-OLT, the patient is doing well with normal systemic blood pressure with excellent hepatic allograft function and without any evidence of tumor recurrence.

Histologic findings of the explanted liver confirmed the diagnosis of malignant paraganglioma with invasion into the inferior vena cava. The surgical margin was negative for any microscopic tumor cell (Fig 4A). The tumor was 7.4 × 4.5 × 3.0 cm in size, and the background liver tissue was normal. The tumor was largely within the inferior vena cava. The tumor cells had moderately abundant granular, amphophilic cytoplasm, and were arranged in well-defined nests defined by delicate fibrovascular septa. The nuclei were round-to-oval and contained variably prominent nucleoli. The nuclear size varied widely, and some were very large and hyperchromatic. The tumor cells demonstrated diffuse and strong positivity for chromogranin (Fig 4B). MIB1 staining was positive in an average of 2 tumor cell nuclei per 400× field.

DISCUSSION

Primary hepatic functioning paragangliomas are extremely rare. Among the 8 cases of primary hepatic paraganglioma cases reported in the current literature, 5 were functioning tumors (Table 1). All 8 cases were treated with hepatic resection; 1 recurred, and there were no available follow up data on 2 patients (Table 1) [4–11]. We report the first case

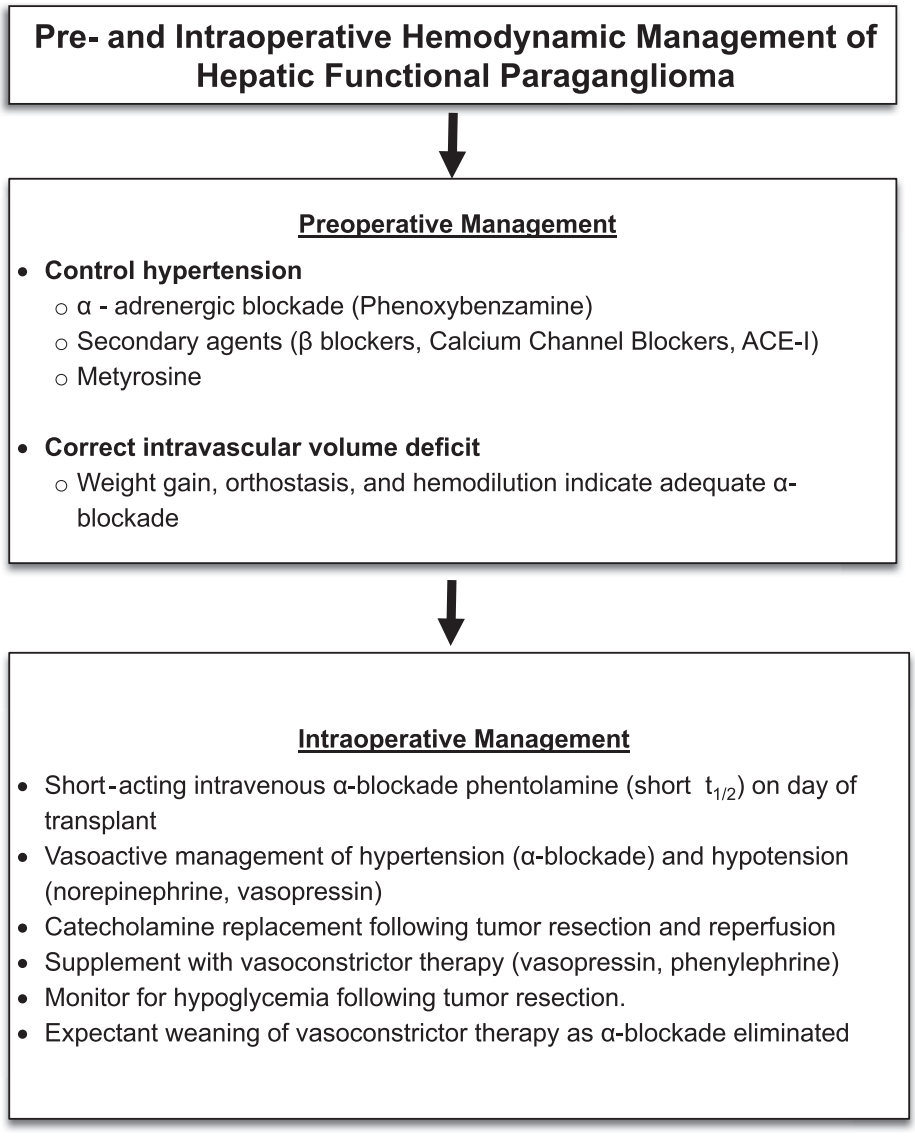

Fig 5. Proposed guidelines for pre- and intraoperative hemodynamic management of primary hepatic functional paraganglioma.

of OLT for an unresectable large centrally located primary hepatic functioning paraganglioma with invasion into the hepatic veins and intrapericardial inferior vena cava. The critical anatomic location of the hepatic tumor required intrapericardial vascular control of the suprahepatic inferior vena cava. We used a transabdominal intrapericardial approach for isolation and vascular control of the suprahepatic inferior vena cava. This approach provided adequate surgical exposure and vascular control and avoided morbidity associated with a median sternotomy. However, it is imperative to ensure adequate postoperative pericardial drainage via drains, pericardial window, or both in order to avoid the development of life-threatening pericardial tamponade secondary to reactive pericardial effusion after closure of the pericardium and diaphragmatic defect [14]. For this case, the diaphragmatic defect was reconstructed using a biological tissue matrix, and a pericardial window between the pericardial and left pleural space was created. The patient did not develop pericardial tamponade. The long-term outcome is excellent with normalized serum metanephrine levels without tumor recurrence.

Our report highlights the importance of a multidisciplinary team approach in the successful management of an unresectable large centrally located primary hepatic functioning paraganglioma. It also underscores the need for meticulous peri- and intraoperative management of extreme hemodynamic swings in patients with functional paraganglioma (Fig 5). Preoperatively, adequate alpha-adrenergic blockade is required. Signs of appropriate

blockade include orthostasis, weight gain, and hemodilution. Intraoperative hemodynamic management focuses on the effects of catecholamines on neohepatic blood flow, microcirculation, and metabolism. Catecholamine replacement is commonly required after both paraganglioma resection and neohepatic reperfusion. Low cardiac output, severe hypotension, or high concentration of endogenous or exogenous vasoconstrictors can adversely affect blood flow to the newly transplanted organ. The short half-life of phentolamine allows for prompt weaning of vasoactive infusion following hepatic allograft reperfusion and avoids prolonged exposure to high dose of vasoconstrictive agents.

To our knowledge, this is the first report showing that OLT is curative for patients with unresectable primary hepatic paraganglioma. For locally advanced unresectable hepatic paraganglioma that involves the intrapericardial vena cava, a meticulous pre- and intraoperative medical management and intrapericardial vascular control of the suprahepatic vena cava during OLT allows for complete extirpation of the tumor and achieves optimal outcome.

REFERENCES

[1] Chrisoulidou A, Kaltsas G, Ilias I, Grossman AB. The diagnosis and management of malignant phaeochromocytoma and paraganglioma. Endocr Relat Cancer 2007;14:569–85.

[2] Gimm O, DeMicco C, Perren A, Giammarile F, Walz MK, Brunaud L. Malignant pheochromocytomas and paragangliomas: a diagnostic challenge. Langenbecks Arch Surg 2012;397:155–77.

[3] Joynt KE, Moslehi JJ, Baughman KL. Paragangliomas: etiology, presentation, and management. Cardiol Rev 2009;17:159–64.

[4] Chang H, Xu L, Mu Q. Primary functioning hepatic paraganglioma: a case report. Adv Ther 2006;23:817–20.

[5] Corti B, D'Errico A, Pierangeli F, Fiorentino M, Altimari A, Grigioni WF. Primary paraganglioma strictly confined to the liver and mimicking hepatocellular carcinoma: an immunohistochemical and in situ hybridization study. Am J Surg Pathol 2002;26:945–9.

[6] Jaeck D, Paris F, Welsch M, et al. Primary hepatic pheochromocytoma: a second case. Surgery 1995;117:586–90.

[7] Khan MR, Raza R, Jabbar A, Ahmed A. Primary nonfunctioning paraganglioma of liver: a rare tumour at an unusual location. J Pak Med Assoc 2011;61:814–6.

[8] Koh PS, Koong JK, Westerhout CJ, Yoong BK. Education and imaging. Hepatobiliary and pancreatic: a huge liver paraganglioma. J Gastroenterol Hepatol 2013;28:1075.

[9] Reif MC, Hanto DW, Moulton JS, Alspaugh JP, Bejarano P. Primary hepatic pheochromocytoma? Am J Hypertens 1996;9:1040–3.

[10] Rimmelin A, Hartheiser M, Gangi A, et al. Primary hepatic pheochromocytoma. Eur Radiol 1996;6:82–5.

[11] You Z, Deng Y, Shrestha A, Li F, Cheng N. Primary malignant hepatic paraganglioma mimicking liver tumor: a case report. Oncol Lett 2015;10:1176–8.

[12] Lenders JW, Pacak K, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA 2002;287:1427–34.

[13] Scott JP, Hoffman GM. Near-infrared spectroscopy: exposing the dark (venous) side of the circulation. Paediatr Anaesth 2014;24:74–88.

[14] Xu J, Hong JC, Busuttil RW. Cardiac tamponade following liver transplantation after intrapericardial control of the suprahepatic vena cava. Liver Transpl 2015;21:339–43.

[15] Hong JC, Yersiz H, Farmer DG, et al. Longterm outcomes for whole and segmental liver grafts in adult and pediatric liver transplant recipients: a 10-year comparative analysis of 2,988 cases. J Am Coll Surg 2009;208:682–9. discussion 689-91.