CASE REPORT

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Leiomyosarcoma of the inferior vena cava. Our experience and a review of the literature

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Abstract

Leiomyosarcoma (LMS) of the inferior vena cava (IVC) is a rare malignant tumor, accounting for 2% of all LMSs. Less than 400 cases have been reported in literature. Computed tomography (CT) is the most accurate imaging method in assessing the location of the tumor within the IVC and magnetic resonance imaging (MRI) accurately identifies its extent and the potential for surgical resection. We present the case of a patient with inferior vena cava leiomyosarcoma (IVCL), for whom the pathological diagnosis was different from the initially expected one, the tumor appearance on pre-operative imaging mimicking renal cell carcinoma. The intraoperative difficulty of approaching renal hilum and IVC was a factor suggesting the vascular origin of the tumor, which was confirmed at pathological analysis. The extensive defect in the IVC after tumor excision led to the decision of complete transverse suturing of IVC, as significant collateral venous circulation was already present. Because IVCL is a rare disease, there is scarce data regarding the prognosis and treatment options. Long-term survival depends on the extent of the surgery. The need of vascular reconstruction is not always mandatory. Despite high recurrence rates, no consensus regarding adjuvant treatment exists yet. A multidisciplinary approach including surgical oncologists and vascular surgeons is mandatory to achieve the best patient outcomes. Perioperative planning, coordination and adherence to oncological techniques are critical.

Keywords: leiomyosarcoma, inferior vena cava, long-term survival, vascular reconstruction.

Introduction

Leiomyosarcoma (LMS) of the inferior vena cava (IVC) is a rare malignant tumor emerging from the smooth muscle cells located in the middle layer of the venous wall, with intra- or extra-luminal growth [1], accounting for 2% of all LMSs [2] and occurring most frequently in middle-aged women [3]. Since Perl & Virchow's first description in 1871 [4], less than 400 cases have been reported in literature [5].

The tumor arises from the tunica media of the blood vessels and can grow either intraluminal, extraluminally or mixed, with one of the patterns being predominant, although the extraluminally type has bed reported as the most frequent [6]. The lesion is included into one of three levels depending on the relation with the hepatic and renal veins, respectively. Zone I represents the infrarenal IVC, zone II the IVC between the hepatic and the renal veins, and zone III the segment above the hepatic veins and up to the right atrium [7], the inferior vena cava leiomyosarcoma (IVCL) most frequently occurring in the middle segment. The tumor can infiltrate both hepatic and renal vessels.

Accurate diagnosis of IVCL needs histological confirmation. The three defining histopathological traits that may predict tumoral behavior (leaning towards a benign or an aggressive pattern) and the overall prognosis are: tumor differentiation, mitotic index and proportion of necrosis [8]. However, these scores may be subjected to errors, as described by Taylor *et al.* [9], where a mitotic index as low as 2 did not anticipate the rapid tumoral progression of the presented case. Two factors would explain the poor prognosis: the tumoral localization and the low degree of tumoral differentiation [10].

IVCL is a malignant slow-growing tumor that produces late clinical manifestations. While upper segment tumors may develop Budd–Chiari syndrome (defined by hepatomegaly, jaundice and ascites) leading to a poor prognosis, tumors located in the middle segment usually present with right upper quadrant pain, or imitate biliary tract diseases, usually associated with better outcomes [11]. Tumor excision within the required oncological surgical margins may often involve extensive IVC repair and reconstruction, associated with increased postoperatively

morbidity and higher mortality. The tumoral growing pace may be steeper or more rampant, showing expansive local invasion and metastasizes more frequently than previously believed [12]. Hematogenous metastases are more frequent, but in advanced stages, IVCL may also spread through the lymphatic system.

Multiple imaging techniques have been assessed and compared for the accuracy of preoperative diagnosis. However, it seems that magnetic resonance imaging (MRI) yields the highest accuracy for IVCL diagnosis, compared to contrast-enhanced computed tomography (CT) [13]. During the first diagnostic workup, a technique comprising of simultaneous contrast agent injection in both pedal veins has been described, using direct multi-detector CT venography, with the great advantage of reaching the maximum vena cava enhancement. The results were comparable with conventional cavography, the gold standard for evaluating the IVC [14], similar achievements being reported for contrast-enhanced magnetic resonance (MR) venography [15].

Five-year disease-free survival and overall survival reported so far are 6% and 55%, respectively [2]. Long-term survival is dependent of the extent and radicality of the surgery. In case recurrence is diagnosed, surgery remains a valid therapeutic option, being effective for controlling disease progression, possibly improving survival [16]. In case complete resection is impossible, combining debulking surgery with radiation therapy provides good palliation [17].

Aim

We hereby present a case of a patient with IVCL, with a number of particular therapeutic and surgical features. In addition, a review of the literature regarding treatment options and prognosis was performed.

Case presentation

A 61-year-old female patient without significant comorbidities presented for a check-up for diffuse abdominal pain. The biological evaluation did not reveal any pathological changes, but ultrasonography identified the presence of a right renal mass. Contrast-enhanced abdominal CT was performed and confirmed the diagnosis of a bulky right renal tumor. Chest CT did not reveal any pulmonary metastasis, thus allowing the final staging as cT3aN0M0 (Figure 1). On the preoperative imaging evaluation, there was no evidence of the invasion of the vena cava, which was medially dislocated, but significant collateral circulation was present. Due to the characteristic appearance of the tumor at imaging scans, pre-operative biopsy was not performed. The patient signed the informed consent prior to publication of this case.

Following the preparation for standard transperitoneal right radical nephrectomy, the surgical intervention was performed in general anesthesia with orotracheal intubation by pararectal prolonged right subcostal approach. One of the main issues during the surgery was the difficult dissection of the renal pedicle, due to the significant collateral vessels and tumoral invasion. Due to this fact, the surgical strategy was modified. First, circumferential dissection of the tumor was performed. The dissection continued towards the renal hilum, where it was observed that the tumor encompassed the renal vessels and a significant segment of the IVC. Therefore, the next step was to isolate the IVC using vessel loops. During the medial dissection of the tumor, the injury of the infra-renal vena cava occurred. In order to perform hemostasis, rapid excision of the remaining tumor and further isolation of IVC was performed. A Satinsky clamp was placed on the lateral wall of the IVC and a suture was performed using Prolene 4/0. Declamping of the IVC was followed by repeating hemorrhage, thus the decision was taken to completely suture the infrarenal IVC in a transverse manner. The blood loss was 2.500 mL and transfusion was required. Postoperatively, the patient presented edema of the inferior limbs, which resolved by conservative approach in five days. Also, a transient kidney dysfunction was present for the first 72 hours.

The macroscopic analysis of the tumor specimen identified the presence of a tumor-adherent tubular vascular formation, which raised the suspicion of the vascular origin for the first time (Figure 2). Grossly, the surgical specimen measured 16.5/11/6 cm and was a block composed of kidney with perirenal fat, adrenal gland and fragment of vena cava. The tumor was located at the upper pole of the kidney, infiltrating the capsule and vena cava wall; it was well circumscribed and measured 9×9×6 cm. Renal vessels and ureter were free of tumor. The cut surface was grey-white, firm, with foci of hemorrhage and necrosis.

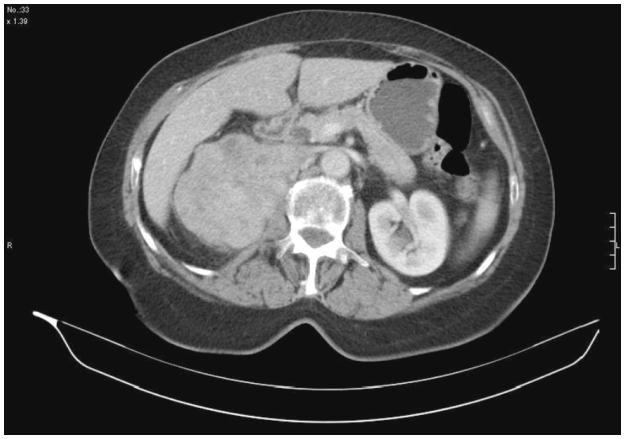

Figure 1 – ***Preoperative computed tomography: right renal bulky tumor.***

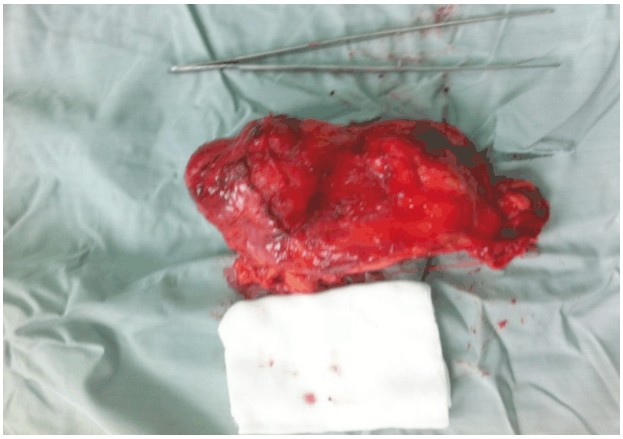

Figure 2 – ***The surgical specimen measured 16.5/11/6 cm and was a block composed of kidney with perirenal fat, adrenal gland and segment of vena cava.***

For positive and differential diagnosis, tumor fragments were collected, fixed in 10% neutral buffered formalin and sent to the Laboratory of Pathology, where they were included in paraffin, then sectioned at the microtome and stained with Hematoxylin–Eosin (HE). Some histological preparations were immunohistochemically stained using anti-alpha smooth muscle (anti-α-SMA) (monoclonal mouse anti-human smooth muscle actin, clone 1A4, 1:100 dilution, Dako), and anti-cluster of differentiation 34 (anti-CD34) (monoclonal mouse anti-human CD34 Class II, clone QBEnd 10, 1:50 dilution, Dako) antibodies.

Microscopically, the tumor consisted of spindle cells with eosinophilic cytoplasm arranged in sheets and whorled, intersecting fascicles (Figure 3A). There was pronounced nuclear pleomorphism and a mitotic rate of 16 mitoses/ 10 high-power fields (HPFs) (field diameter was 0.5 mm), also with atypical mitosis (Figure 3B). In some areas of the tumor, small areas of necrosis and inflammatory infiltrate have been identified (Figure 3C). The tumor cells were strongly positive for α-SMA (Figure 3, D and E). CD34, by revealing the endothelium, showed an intense vascularization of the tumor, the vessels being formed mainly of arterioles, capillaries and venules, some of the capillaries being identified as vessels of angiogenesis (Figure 3F).

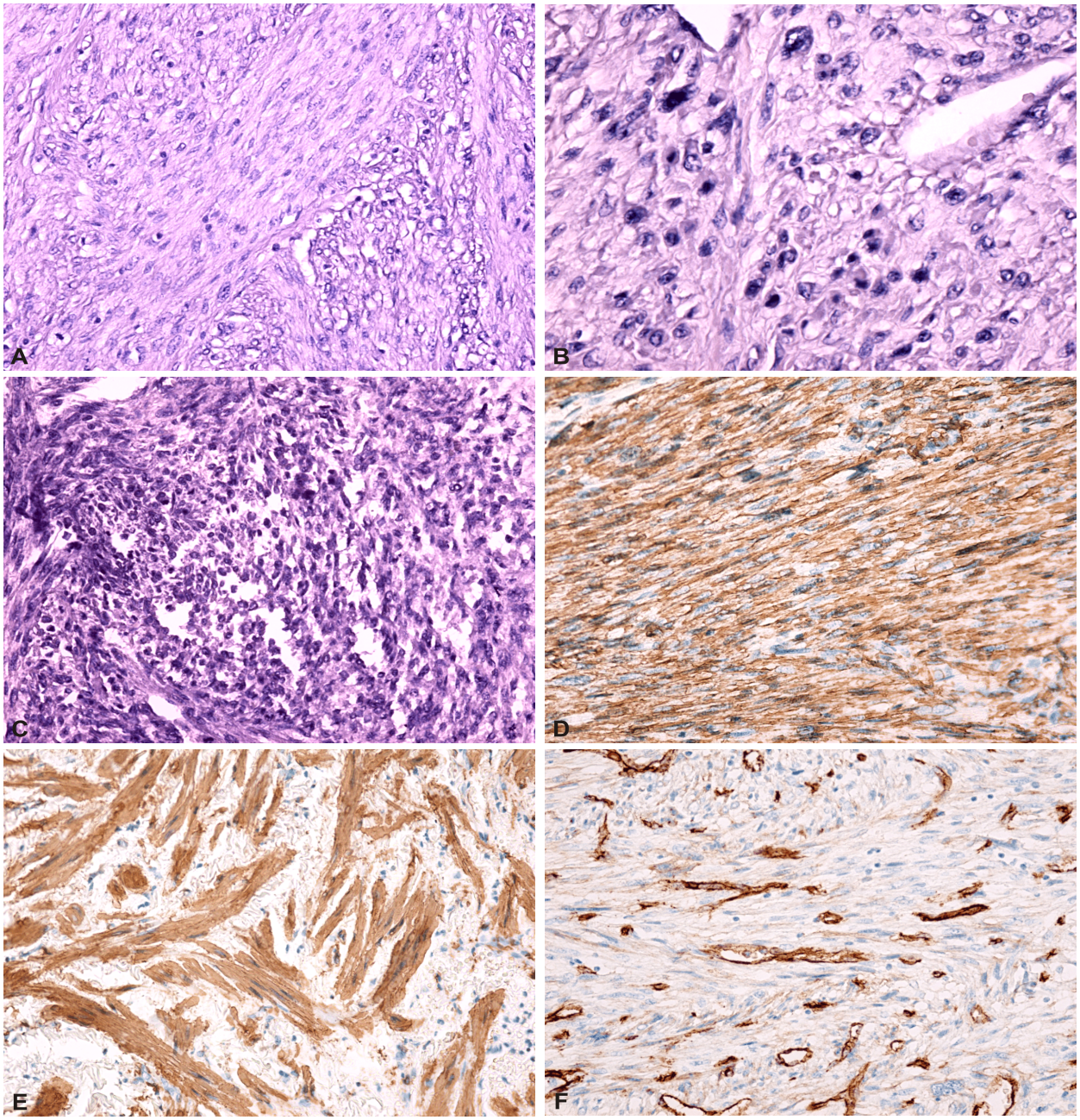

Figure 3 – ***(A) Histologically, the tumor consisted of spindle cells with eosinophilic cytoplasm arranged in sheets and whorled, intersecting fascicles; (B) There was pronounced nuclear pleomorphism and a mitotic rate of 16 mitoses/10 HPFs (field diameter was 0.5 mm), also with atypical mitosis; (C) Area of tumor necrosis with a moderate intratumoral inflammatory infiltrate; (D) Tumor cells organized in layers, with positive reaction to α-SMA; (E) Tumor cells organized in bundles with various orientations, with positive reaction to α-SMA; (F) Tumor area with an increased microvascular density. HE staining: (A and C) ×200; (B) ×400. Immunomarking with anti-α-SMA antibody: (D and E) ×200. Immunomarking with anti-CD34 antibody: (F) ×200. HPFs: High-power fields; α-SMA: Alpha-smooth muscle actin; HE: Hematoxylin–Eosin; CD34: Cluster of differentiation 34.***

Macroscopic and microscopic aspects allow us to support the hypothesis that the origin of the tumor was the smooth muscles in the wall of the IVC.

During the four years of follow-up, no recurrent lesions were identified on the imaging, the patient being considered disease-free. Significant collateral venous circulation was described because of the suturing of the IVC (Figure 4).

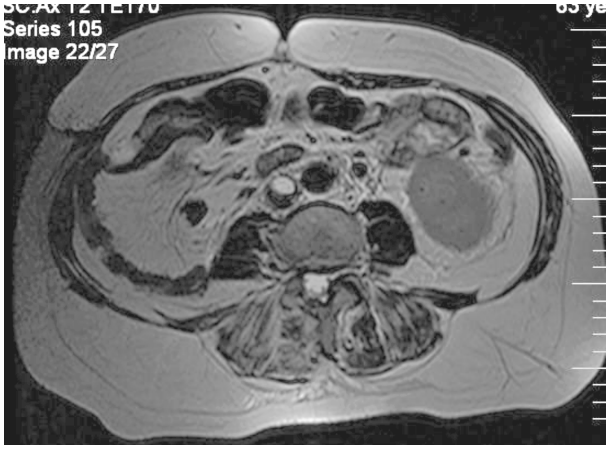

Figure 4 – ***The aspect of postoperative MRI: no recurrent lesions are detected, and numerous collateral venous circulation elements are present after suture of IVC. MRI: Magnetic resonance imaging; IVC: Inferior vena cava.***

Discussions

IVCLs are rare malignant tumors, often presenting very late with non-specific symptoms, like diffuse abdominal pain in the case hereby presented. A limited number of these cases have been described so far, occurring most frequently in middle-aged women. Only few of them have intracardiac propagation and surgery is rarely undertaken for their treatment [18].

A combination of imaging modalities, such as CT or MRI, is essential for treatment choice and planning [19]. The most characteristic CT sign for predicting the origin of IVCL is a poorly depictable IVC at the level where there is maximal contact with a retroperitoneal located tumor. The IVC origin of the tumor can be excluded in the presence of a negative embedded organ sign [20]. Knowledge of these CT characteristics represents the basis of a thorough preoperative planning. In a retrospective study [21], the imaging of primary tumor from 18 non-IVCLs and 19 IVCLs and follow-up imaging studies were reviewed; the authors found no significant difference between the imaging characteristics of these patients and the metastatic pattern of non-IVCL and IVCL. From a radiologist's perspective, non-IVCL behaves similar to IVCL. Survival of the patients with IVCL is no worse than of patients with leiomyosarcomatous lesions of other origin [22]. IVCL and non-IVCL exhibit similar outcomes in terms of postoperative course and survival [23].

In our case, there was no imaging evidence of the invasion of the vena cava, which appeared medially dislocated, but there was a significant collateral circulation. The tumor was located at the upper pole of the kidney, infiltrating the capsule and vena cava wall; it was well circumscribed and measured 9/9/6 cm. The macroscopic analysis of the tumor specimen from our patient identified the presence of a tumor-adherent tubular vascular formation, which raised the suspicion of the vascular origin for the first time.

When confronted with an imagistic finding, such as a tumor-like formation that occupies the IVC, differential diagnosis must be made with other pathologies that have an accentuated venous tropism and during their natural evolution might involve the vena cava. Renal cell carcinoma should always be considered when it comes to IVC tumoral extension. Between 5% and 15% of renal cell neoplasms develop a tumoral thrombus that penetrates the renal vein and can occupy the IVC up to the right atrium, in 1% of the cases [24]. Usually, the histopathological result of renal cell carcinoma is the most frequent scenario, especially when associated with a voluminous renal mass. However, as described in our case, other rare histological etiologies can be present. Another malignancy that can be held accountable for interesting the IVC is hepatocellular carcinoma, most commonly affecting the portal vein, but in up to 4% of the cases, it invades the IVC and extends to the right atrium, possibly causing pulmonary embolism [25]. An abdominal contrast-enhanced CT scan can differentiate between a pathology primarily emerging from the liver *versus* the kidney, as well as the final histological result. Regarding tumors that are most likely to have a benign evolution, cases of renal angiomyolipoma [26] and pheochromocytoma [27] have been reported to express an aggressive pattern and to extend into the IVC, especially if they are right-sided. From a radiological point of view, intraluminal tumor-like images can be the result of poor mixing of the contrast agent from the renal veins with the blood coming from the lower limbs. This effect is seen preponderantly in patients with congestive heart failure [28].

From a different perspective, IVCL should be differentiated from LMSs arising from surrounding structures, mainly from the kidney and the retroperitoneum. Renal LMSs develop from the renal structures that have smooth muscle layers, such as the renal capsule, pelvis and vein. The most frequent site is the renal vein [29], being also the most common location for extracaval LMSs, followed by renal capsule [30] and renal pelvis [31]. Fifteen percent of all soft tissue sarcomas are located in the retroperitoneum, 20% of them being LMSs. The primary curative treatment is represented by surgery, while radiation therapy and chemotherapy, although associated with surgery or stand-alone therapy in advanced cases, cannot establish the same outcomes and long-term survival rates as full tumoral excision [32]. In order to differentiate a primary IVCL from the fore mentioned sites, preoperatively contrast-enhanced CT scan is required, as well as immunohistochemical staining of the specimen. In the presented case, the tumor was strongly positive for α-SMA, as well as CD34, an endothelial marker, showing its vascular origin. With the renal vessels and collecting system free of disease, we can state that the primary site of this tumor is the IVC.

Despite recent research regarding different therapeutic strategies for IVCL, surgical resection with a tumor-free

margin (1 cm) seems to be the approach with the highest probability to cure this disease. Unfortunately, only a small percentage of patients are eligible to undergo surgical intervention. The optimal surgical management remains a controversy [19]. The lack of studies assessing large series of IVCL treated in the same center and lack of long-term follow-up lead to uncertainties regarding the best treatment algorithm [33]. Preoperative external-beam radiation may facilitate a resection with negative surgical margins [34]. Also, cross-sectional imaging, by allowing to establish the exact location and IVC extension of the tumor, plays a vital role in determining the resectability and planning the surgical approach [35].

A review of the literature including 142 patients [33] showed approximately similar percentages of tumors originating from the three segments of IVC. In 49 cases, the tumor arose from the infrarenal segment of the IVC. In 59 patients, the IVCL had the origin in the segment between the renal pedicle and hepatic veins, whereas in 34 patients the tumor was located between the hepatic veins and the right atrium. In 82 cases, the tumor was radically resected, leading to improved long-term survival (27.9% at five years and 14.2% at 10 years). The survival of the patients with middle segment IVCL was significantly higher as compared to lower-segment tumor (48.3% *vs.* 9.3% at five years). Good prognosis was associated with the presence of abdominal pain and the lack of a palpable tumor at diagnosis. Despite the high recurrence rate (52.4% at two years), extensive radical resection of IVCL was the main predictor for a potentially curative approach.

For our patient, the lateral wall of the IVC was initially clamped and the suture of the vein wall was performed, but the hemorrhage reappeared and the transverse suture of the infrarenal portion of IVC was performed as the only solution for vital hemorrhagic risk.

Although the IVCL is surgically removed, this does not necessarily guarantee a long-term survival for the patient. Furthermore, complementary therapies, such as radio- and chemo-therapy often prove insufficient oncological control. The recurrence of the tumor after previous initial surgical resection is commonly diagnosed and occurs in the majority of the patients [36]. As a particularity, in our case, during a follow-up of four years, no recurrence of the tumor was identified, in comparison with other reported cases who underwent more than 20 surgical reinterventions after the primary surgery.

The optimal management of the IVC after tumor resection is still a subject under debate. Primary repair, ligation and IVC reconstruction have been utilized with different success rates [37]. The need of vascular reconstruction is not always mandatory [38]. The necessity to perform a large resection for a primary IVCL requires the segmental excision of IVC in some cases. Reconstruction of the IVC is not always necessary when the tumor is located below the level of the hepatic veins [34]. Even in the occurrence of lower-extremity edema secondary to the ligation of the IVC, this adverse situation is well tolerated. Other common post-operative complications are represented by acute renal failure, which is usually transient, and chylous leak, which can be managed with internal or external drainage.

Intraoperatively, in our case, an extremely abundant venous collateral circulation was identified. Postoperatively, our patient presented edema of the inferior limbs, resolved by conservative approach in five days.

In a study on three patients [6], the mean age at diagnosis of IVCL was 60.3 years (range 43–78 years), while the mean tumor size was 12.2 cm. The authors reported a mean operative time of 320 minutes and a mean blood loss of 1300 mL. The average length of hospital stay for these patients was 8.67 days, with a maximum of 12 days. Our patient experienced 2500 mL intraoperative blood loss, which was compensated by transfusion.

When performed, the reconstruction of an IVC defect after surgical resection can lead to significant postoperative complications, such as venous thrombosis or infection of the graft [39]. The reconstruction can be performed using autologous venous grafts from the patient's own left internal jugular and left external iliac vein. The two veins are incised along their axis and are sutured together to form a wider tube graft to match the IVC defect [39].

A retrospective review of patients diagnosed with IVCL and treated during a 10-year period showed that neoadjuvant radiotherapy, followed by extensive surgical resection led to complete local control. The use of superficial femoral vein for IVC reconstruction was proven to be safe, with low associated morbidity. Long-term follow-up yielded good results, with the authors reporting that all patients were alive at a median follow-up of 37 months [40].

Although initial results of surgical resection of IVCL are encouraging, the majority of patients experience recurrence. However, as reported by several authors, long-term survival is possible [41]. The predictors of survival after surgical excision of IVCL include margin status, tumor size and the radicality of the resection [2]. On the other hand, in a study of 218 patients enrolled into *The International Registry of IVCL*, from which 120 patients underwent a radical resection of the IVCL, an extended venous resection in IVCL did not influence neither local recurrence rate nor long-term outcome [42].

There were 143 reports of IVCL in Japan. In 31% of them, IVC was not reconstructed [43]. In a series of five patients with IVCL treated at two Chinese centers, the authors report no IVC related postoperative complications, although the surgeries included multiorgan resection, without IVC reconstruction [19].

The first case of IVCL, involving all three segments of the abdominal IVC (infrarenal, suprarenal and retrohepatic vena cava) along with right kidney, right adrenal as well as right hepatic vein and left renal vein, treated without IVC reconstruction, was described in a study [44]. IVCL was resected completely and despite its extent and concomitant involvement of surrounding organs, it had a favorable response combining prolongation of survival and satisfactory quality of life.

Conclusions

IVCL is a treatable malignancy, but remains a challenge for surgeons. Imagistic studies need to be performed preoperatively in order to correctly assess its extension

and properly plan the surgery. Despite recent research regarding the best therapeutic strategy for IVCL and the high rate of recurrence, surgical resection appears the only potentially curative treatment. A multidisciplinary approach including surgical oncologists and vascular surgeons ensures maximal resection with functional reconstruction to achieve the best patient outcomes. Perioperative planning, coordination and adherence to oncological techniques are critical.

Conflict of interests

Authors declare that there is no conflict of interests.

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