CASE REPORT

Primary adrenal leiomyosarcoma with inferior vena cava extension in a 70-year-old man

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SUMMARY

Primary adrenal leiomyosarcoma, a malignant soft tissue tumour originating from the smooth muscle of the inferior vena cava and adrenal vein, is rarely described in the literature. Cases are often diagnosed at an advanced stage as the tumour is not hormone-producing. We describe a 70-year-old man who presented with lower extremity swelling and abdominal varices and was subsequently found to have a large adrenal mass on imaging. Our case is among the few reported primary adrenal leiomyosarcomas in which a CT-guided biopsy was used to aid in diagnosis.

BACKGROUND

Leiomyosarcomas are malignant soft tissue tumours of smooth muscle origin. Traditionally, leiomyosarcomas are most commonly associated with the uterus, but they also frequently occur in the bowel, vasculature and dermis.[1] Primary adrenal leiomyosarcomas (PAL) are extremely rare variants of these soft tissue neoplasms with 35 cases reported in the western literature, including the patient presented in this report. PAL is thought to originate from the smooth muscle wall of the central adrenal vein and its branches.[2] Because PAL does not produce hormones, symptoms generally do not manifest until the tumour has reached an advanced size. Diagnosis of PAL is usually made via histological and immunohistochemical evaluation after surgical resection. We herein describe a case of a 70-year-old man who presented with lower extremity swelling and was diagnosed with PAL via a CT-guided biopsy prior to surgical resection.

CASE PRESENTATION

The patient is a 70-year-old man who originally presented to his primary care physician with abdominal varices and lower extremity swelling. CT demonstrated a 12.2 cm mass arising from the right adrenal gland with extension into the inferior vena cava (IVC). A CT-guided biopsy was performed, and the subsequent pathology was consistent with leiomyosarcoma. Microscopic examination revealed a highly cellular atypical smooth muscle neoplasm with 40% proliferation on ki-67 stain; the tumour also stained strongly for vimentin and desmin and negatively for S-100 further supporting the diagnosis. The patient was accordingly scheduled for surgical resection.

INVESTIGATIONS

Gross examination of the surgical specimen (figure 1) demonstrated a 9.0×7.5×4.3 cm tan multilobulated mass which obliterated the adrenal gland and was adherent to the kidney; a tissue plane could not be identified. The right intracaval margin did not demonstrate tumour. Histological examination of the neoplasm demonstrated a hypercellular spindle cell neoplasm. The cells were cigar-shaped, running in parallel fascicles to one another, and demonstrated small, prominent nucleoli (figure 2). The tumour demonstrated strong, diffuse immunoreactivity to smooth muscle actin and caldesmon (figures 3 and 4), supporting the diagnosis of leiomyosarcoma. The final diagnosis rendered was that of a leiomyosarcoma, high grade (grade 3) with negative margins. There was no evidence of vascular invasion seen. Microscopic analysis of the mass divulges a stage pT2b, grade 3 leiomyosarcoma with no lymphovascular invasion and 1 cm negative surgical margins.

TREATMENT

The surgery took place in April 2017 under the diagnosis of retroperitoneal leiomyosarcoma with the invasion of the IVC. A venogram was initially performed and revealed that the IVC was the only patent to the level immediately below the origin of the renal veins. The venogram also showed significant collateralisation, most notably a prominent vessel posterior to the expected course of the IVC draining directly into the right atrium. The patient was subsequently placed in the modified flank position to proceed with resection. Exposure of the right flank demonstrated significant varices in the mesentery of the hepatic flexure and an adrenal mass densely adherent to the upper pole of the right kidney, the renal hilum and the adjacent renal vasculature. It was determined that the right kidney could not be safely dissected from the mass and the decision was made to perform a total nephrectomy and adrenalectomy. Careful dissection established an appropriate plane, but the IVC was significantly thrombosed and tumour adhesions were noted on the inferior surface of the liver.

Tumour extension into the IVC and the consequent thrombosis was then addressed. Exposure and identification of the suprahepatic IVC and portal triad were first performed for prompt control of potential IVC bleeding. The intrahepatic IVC above the tumour and its accompanying draining vessels (most notably a small vein draining the caudate lobe

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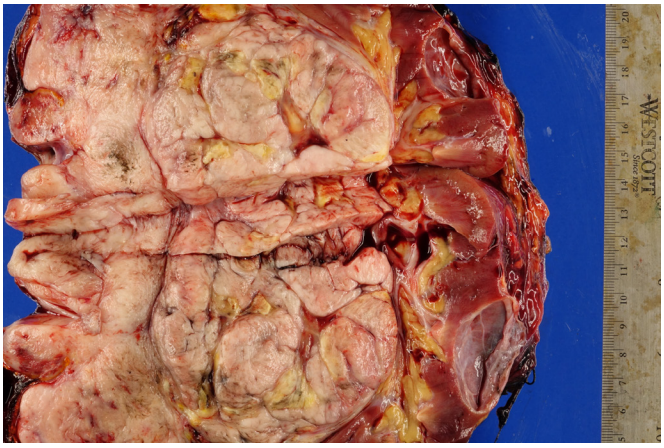

Figure 1 Gross examination of the surgical specimen.

of the liver) were identified and ligated with silastic vessel loops. The infrahepatic IVC below the level of the tumour, the adjacent renal veins and the large posterior venous collateral (previously noted on venography) were then ligated and a venotomy was made at the base of the tumour. The IVC was then transected just above the posterior collateral drainage and the tumour and kidney were subsequently removed en bloc as a specimen. Chronic adherent thrombus noted on the margin of the vessel was removed via thromboendarterectomy techniques, and the resulting specimen was sent to pathology to document sufficient margins.

OUTCOME AND FOLLOW-UP

Following recovery from surgery, the patient had the resolution of his symptomatic lower extremity swelling and abdominal varices. However, at 1-year follow-up, pulmonary metastases were discovered, and the patient passed in June 2018. The patient mortality occurred approximately 14 months after diagnosis.

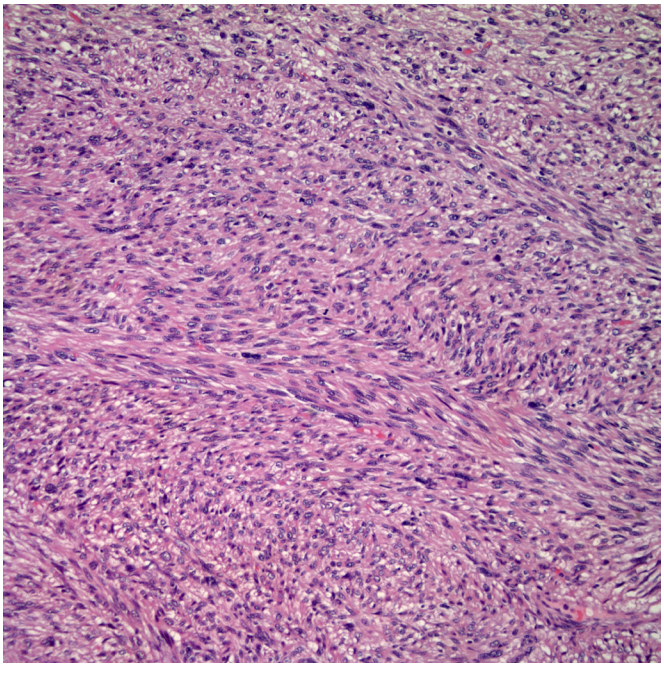

Figure 2 The cells are cigar shaped, running in parallel fascicles to one another, and demonstrate small, prominent nucleoli.

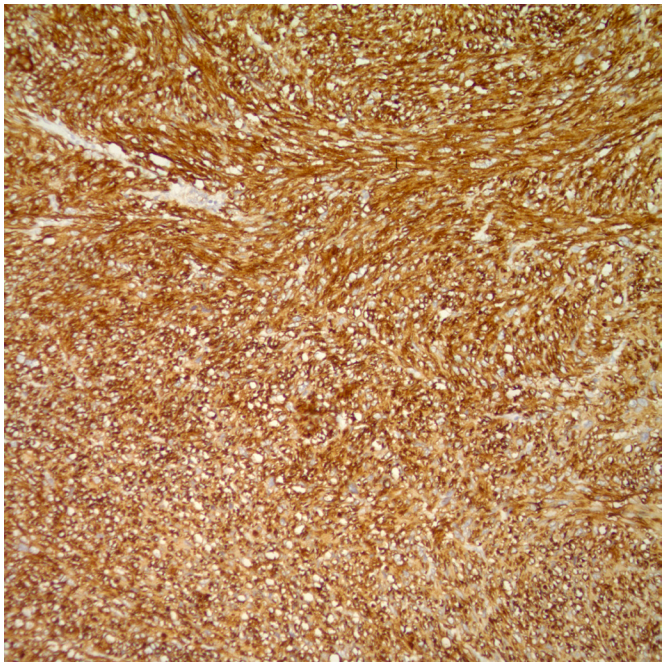

Figure 3 The tumour demonstrates strong, diffuse immunoreactivity to smooth muscle actin.

DISCUSSION

PAL is an extremely rare neoplasm of mesenchymal origin that is believed to originate from the smooth muscle wall of the IVC, central adrenal vein and its tributaries.[2] To our knowledge, there are 35 cases reported in the English literature, including the patient presented in this report. Below, we describe the clinical and pathological characteristics of PAL by providing a thorough analysis of known cases.

PAL appears to be most prevalent after the fifth decade with an average age of presentation of 55.6±15 years. The one

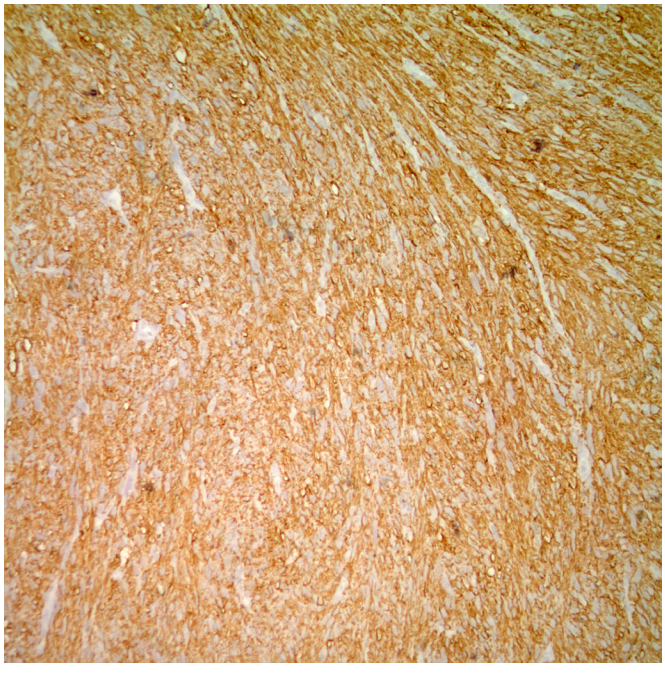

Figure 4 The tumour also demonstrates strong, diffuse immunoreactivity to smooth muscle caldesmon.

Table 1 Summary of patient/tumour characteristics, treatments and outcomes of known cases of PAL in the literature[2–6 9 10 13 15 17–41]

Study	Age (years)	Gender	Location	Size (cm)	Extension	Presentation	Treatment	Outcome
Choi and Liu	50	F	L	16	No	Flank pain	Adx+partial Nx	12 months DFS
Lack *et al*	49	M	R	11	No	Flank pain	Adx+partial Nx	9 months, metastasis
Zetler *et al*	30	M	L	11	N/D	N/D	Adx	20 months DFS
Boman *et al*	48	M	R	2	N/D	Cachexia	None	N/D
Boman *et al*	29	M	L	0.8	N/D	Cachexia	None	N/D
Etten *et al*	73	F	R	27	IVC	IVC syndrome	N/D	3 weeks, deceased
Matsui *et al*	61	F	R	N/D	IVC+right atrium	Flank pain	Adx+Nx+thrombectomy	1 month, deceased
Lujan and Hoang	63	M	R	25	AO+PM	Enlarging RUQ mass	CT+Adx+ Nx+hepaticlobectomy+ cholecystectomy	Deceased shortly after surgery
Thamboo *et al*	68	F	R	13	No	Flank pain	Adx+Nx	12 months DFS
Linos *et al*	14	F	B	3.5	No	N/D	N/D	N/D
				4		N/D	N/D	N/D
Kato *et al*	59	M	L	10	IVC	Flank pain	Adx+Nx+thrombectomy	6 months, deceased
Wong *et al*	57	M	L	N/D	IVC+common iliac arteries	Groin pain, cold feet	Adx+Nx+thrombectomy	6 months, recurrence
Candanedo-Gonzalez *et al*	59	F	L	16	AO	Flank pain	Adx+CT+RT	36 months, metastasis
Lee *et al*	49	M	L	3	No	Flank pain	Adx	10 months DFS
Mohanty *et al*	47	F	L	10	No	Abdominal pain	Adx+Nx+RT	9 months, metastasis
Wang *et al*	64	F	R	14	IVC+right atrium	B/l LEE, productive cough	Adx+thrombectomy	10 months DFS
Goto *et al*	73	F	R	8	AO	Flank pain	Adx+Nx	10 months DFS
Mencoboni *et al*	75	F	R	8	No	Flank pain+abdominal pain	Adx	12 months DFS
Van Laarhoven *et al*	78	M	L	N/D	Multiple metastases	N/D	RT	11 days, deceased
Hamada *et al*	62	F	B	8	No	Flank pain	Bil Adx+CT+RFA+RT	16 months, deceased
				4	No			
Karaosmanoglu and Gee	63	M	R	N/D	IVC	B/l LEE+abdominal pain	CT	3 months, deceased
Shao *et al*	66	M	L	10	Renal vein	N/D	Adx	18 months DFS
Kanthan *et al*	28	F	L	16	No	Abdominal pain	Adx+Nx+partial Nx	N/D
Deshmuku *et al*	60	F	L	5	No	Flank pain	Adx	21 months DFS
Gulpinar *et al*	48	M	R	11	No	Lower Urinary Tract Symptoms	Adx	8 months DFS
Ozturk	70	F	R	8	IVC	Flank pain	Adx+cavatomy+CT	6 months, metastasis
Lee *et al*	28	M	R	15	No	Flank pain+weight loss	Adx	18 months DFS
Bhalla *et al*	45	M	R	11	Multiple metastases	Flank pain	CT	9 months, metastasis
Wei *et al*	57	F	L	8	No	None	Adx	29 months DFS
Zhou *et al*	49	F	L	6	No	Flank pain+abdominal pain	Adx	6 months DFS
Onishi *et al*	34	M	R	5.2	IVC	Flank pain	Adx+Ldx	No recurrence
Nagaraj *et al*	61	M	L	16	No	Flank pain	Adx	N/D
Alam *et al*	35	F	L	8.5	No	Flank pain	Adx	N/D
Aoki *et al*	81	F	R	7	No	Abdominal pain	Adx	12 months, deceased
Doppalapudi	70	M	R	9	IVC	B/l LEE+abdominal varices	Adx+Nx cavatomy+thrombectomy	12 months, deceased

Adx, adrenalectomy; AO, adjacent organ; B, bilateral; B/l LEE, bilateral lower extremity oedema; CT, chemotherapy; IVC, inferior vena cava; N/D, not disclosed; Nx, nephrectomy; PAL, primary adrenal leiomyosarcoma; PM, pulmonary metastases; RFA, radiofrequency ablation; RT, radiation therapy; RUQ, right upper quadrant.

outlier found was a 14-year-old girl with AIDS who presented with bilateral tumours.[3] While the precise aetiology of PAL is not known, it has been reported that incidence may be associated with positive HIV/EBV serology.[2 4–7] This may explain the especially early presentation seen in this one patient. The most common symptom at presentation is ipsilateral flank pain occurring in roughly half of those afflicted. The incidence of PAL does not exhibit gender predilection with a roughly even distribution of cases noted between males and females. In addition, there does not appear to be any laterality preference, as right-sided and left-sided tumours occur with similar frequency (table 1).

Symptoms associated with PAL appear to be primarily attributed to mass effect and local invasion. For instance, those patients with invasion or malignant thrombosis into the IVC often presented with lower extremity oedema, spider angiomata and/or abdominal varices. In fact, vascular invasion at presentation is common, occurring in 26.5% of reported cases. Early vascular invasion seen with PAL may be attributed to its smooth muscle wall origins in the IVC and central adrenal vein. Additionally, because symptoms of PAL are presumably due to mass effect, tumour size at presentation is often large with an average size of 10±5.9 cm.

Diagnosis of PAL is generally made via surgical pathology. Preoperative diagnosis is difficult because there is a lack of identifiable biomarkers or specific endocrinological changes associated with this neoplasm. Consequently, advances in urine steroid metabolomics and steroid profiling may not have a great impact in detecting PAL; the value of this diagnostic tool appears to be greater in differentiating adrenocortical carcinoma (ACC) from adrenocortical adenoma (ACA).[8] Neuron-specific enolase has been suggested as a potential biomarker for early detection of PAL, but lack of replicable results has hampered its value as a suitable tumour marker.[2 9] In addition, there are no radiological features on CT or MRI that distinguish PAL from other adrenal malignancies. However, radiological studies are still useful for assessing resectability and metastasis. Imaging may also be valuable for distinguishing between potentially benign and malignant lesions by evaluating growth rate (via serial studies) and tumour size. The current guidelines for the management of adrenal tumours recommend against further imaging for incidentalomas under 4 cm of size with benign characteristics, although this is a weak recommendation. In fact, this cut-off of 4 cm to delineate potential malignancy (34%–61% specific) is challenged by Iniguez *et al*, in which only 31% of adrenal tumours above 4 cm were malignant. However, two notable risk factors for malignancy in this study were larger tumour size (7 cm) and non-incidental mode of discovery, suggesting that imaging still serves an integral role in the evaluation of adrenal tumours.[10–12] Additionally, we utilised radiological guidance in the form of a CT-guided biopsy to ascertain a tissue diagnosis for our patient prior to surgical resection. A core biopsy prior to surgical diagnosis has been reported in only two previous PAL cases, and we believe that it should be undertaken whenever feasible as an accurate preoperative diagnosis can be useful in surgical planning.[3 13] It must be stressed, however, that prior to biopsy, a thorough initial evaluation should include clinical, hormonal and radiological studies. This is especially true in cases of pheochromocytoma, in which improper manipulation of the tumour can lead to catecholamine-induced hypertensive crisis and mortality. In addition, while a CT-guided biopsy is generally discouraged in the evaluation of ACC and pheochromocytomas, it has shown potential value in the diagnosis of malignant adrenal tumours in which surgery may not be the first step for treatment (lymphomas).[14] Due to the non-hormone-producing nature of our reported tumour and the low index of suspicion of ACC and pheochromocytoma on imaging, a CT-guided biopsy was deemed a logical step prior to further intervention.

Ultimately, histopathological diagnosis is needed to confirm the diagnosis. Histopathological evaluation of PAL reveals highly cellular spindle cells with eosinophilic cytoplasm and elongated, centrally located nuclei. Immunohistochemical staining shows reactivity to various smooth muscle markers including desmin, SMA (smooth muscle actin), vimentin and smooth muscle heavy chains. Leiomyosarcomas are also characteristically negative for S-100, alfa-inhibin and CD117.[15] Our analysis of current literature shows that SMA (73.5%), desmin (50%) and vimentin (47%) are the most common markers associated with PAL (table 2). Pleiomorphic subtypes are rare with five known cases (14.7%) and may show variable expression of these markers. As previously mentioned, a core biopsy of the tumour was sufficient in making the diagnosis in our patient before surgical resection was performed. Pathology analysis revealed a highly cellular atypical smooth muscle neoplasm that stained strongly for desmin and vimentin and negatively for S-100.

The mainstay of PAL treatment is radical surgical excision of the mass. In fact, the most important prognostic factor for survival is the ability to achieve microscopically negative margins during resection.[15] Other important prognostic factors include tumour size, grade, location, presence of venous thrombosis and distant metastasis. Our analysis of the 35 reported cases of PAL particularly highlights the potential importance of patient age and tumour size on clinical outcomes. For instance, the average age of patients experiencing recurrence or mortality (61.9±10.9 years) was older than those experiencing disease-free survival (53.1±15.7 years). Similarly, the average tumour size at presentation was also larger in deceased individuals and those experiencing recurrence (13.3±6.8 cm) when compared with those who are disease free (9.5±4 cm). While noteworthy, these findings are not statistically significant (p=0.095 and 0.0938, respectively).

The definitive role of chemotherapy and radiotherapy is unclear. There seems to be a potential role for radiotherapy in the treatment of PAL as radiation is often utilised as adjuvant therapy in many soft tissue sarcomas of the extremities.[16] In one case reported by Mohanty *et al*, radiotherapy was justified due to the extreme degree of pleomorphism and high mitotic activity

Table 2 Pathologic characteristics of known cases of PAL in the literature[2–6 9 10 13 15 17–41]

Study	Pathology
Choi and Liu	N/D
Lack *et al*	Vimentin/actin/SMA+
Zetler *et al*	SMA+
Boman *et al*	SMA/HHF35/vimentin/desmin+
	SMA/HHF35+
Etten *et al*	SMA+
Matsui *et al*	SMA+
Lujan and Hoang	Pleomorphic
Thamboo *et al*	SMA/vimentin/actin/desmin+
Linos *et al*	SMA/viminten/actin/HHF+
Kato *et al*	Pleomorphic+SMA/desmin/vimentin+
Wong *et al*	N/D
Candanedo-Gonzalez *et al*	Pleomorphic+SMA/desmin/vimentin+
Lee *et al*	Desmin+
Mohanty *et al*	Pleomorphic+desmin/calpinin/actin+
Wang *et al*	SMA/desmin+
Goto *et al*	SMA/NSE+
Mencoboni *et al*	SMA/desmin/actin+
Van Laarhoven *et al*	SMA/actin/vimentin+
Hamada *et al*	SMA+
Karaosmanoglu and Gee	Actin/vimentin/desmin/keratin+
Shao *et al*	SMA/desmiin+
Kanthan *et al*	Pleomorphic+SMA/vimentin+
Deshmuku *et al*	SMA/vimentin/desmin+
Gulpinar *et al*	SMA/vimentin+
Ozturk *et al*	SMA/desmin+
Lee *et al*	SMA/desmin+
Bhalla *et al*	Desmin/actin+
Wei *et al*	SMA/vimentin/actin/desmin+
Zhou *et al*	SMA/desmin/vimentin+
Onishi *et al*	SMA+
Nagaraj *et al*	Desmin/vimentin+
Alam *et al*	N/D
Aoki *et al*	SMA/vimentin+
Doppalapudi	Vimentin/desmin+

PAL, primary adrenal leiomyosarcoma; SMA, smooth muscle actin.

seen in the index tumour.[9] Neoadjuvant chemotherapy seems to warrant lesser consideration. Paclitaxel was utilised preoperatively in Lujan and Hoang but continued growth of the adrenal mass was noted prior to resection.[3] Chemotherapy should be considered as a palliative measure in metastatic disease, however. Although leiomyosarcomas are known to be slow growing with late metastasis, the prognosis is generally poor and local recurrence is common.

Learning points

- Primary adrenal leiomyosarcoma (PAL) is an extremely rare neoplasm of mesenchymal origin that arises from the smooth muscle wall of the inferior vena cava (IVC), central adrenal vein or its tributaries.
- Patients most commonly present with ipsilateral flank pain and symptoms generally develop due to mass effect and local invasion. There is no gender or laterality predilection.
- Discovery of a mass is generally made via cross-sectional imaging (CT or MRI) and treatment generally consists of surgical resection of the adrenal gland and the remaining tumour burden with special consideration for consolidation radiation in pleomorphic cases.
- Diagnosis is made via histopathological evaluation and immunohistochemistry. Histopathological evaluation of PAL reveals highly cellular spindle cells with eosinophilic cytoplasm and elongated, centrally located nuclei. Immunohistochemical staining shows reactivity to various smooth muscle markers including desmin, smooth muscle actin, vimentin and smooth muscle heavy chains.
- Although PAL grows slowly with late metastasis, prognosis is poor and recurrence is common.

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Contributors SD: wrote the vast majority of the manuscript and performed a thorough literature regarding the topic, embedding a synthesis of current data in the discussion. TS: edited the manuscript and wrote the abstract for the paper. VAF: wrote the pathology-related portions of the manuscript. VB: performed the surgery, acquired next of kin consent for this case report and edited the manuscript.

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