

Primary Adrenal Leiomyosarcoma: Clinical, Radiological, and Histopathological Characteristics

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Primary adrenal leiomyosarcoma (PAL) is a rare, high-grade proliferating mesenchymal tumor with a considerable risk of metastasis, deriving from the smooth muscle wall of a central adrenal vein, or its tributaries. Roughly 40 patients with PAL have been reported in the literature. Herein, we present 3 patients with incidentally discovered PAL, along with an overview of the current knowledge on the clinical, radiological, and histopathological characteristics of PAL.

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Primary adrenal leiomyosarcoma (PAL) is a rare mesenchymal tumor that derives from the smooth muscle wall of a central adrenal vein or its tributaries [1, 2]. PAL is a high-grade proliferating tumor with a considerable risk of metastasis. PAL does not express or secrete adrenal hormones and characteristic tumor biomarkers have not been identified. Hence, a preoperative diagnosis of PAL is difficult, and the tumor is often discovered at an advanced stage.

The first patient with PAL was reported by Choi and Liu in 1981 [3]. To our knowledge, some 40 additional cases have since then been reported in the literature. Herein, we present 3 patients with incidentally discovered PAL, along with an overview of the current knowledge of the clinical, radiological, and histopathological characteristics of PAL.

Subject #1

A 72-year-old man, with a previous medical history of mild hypertension, presented with a sudden onset abdominal pain and a feeling of uneasiness. He had no history of weight loss or fever. Computed tomography (CT) of the abdomen, performed due to suspected bowel perforation, revealed mild diverticulitis and a 4 × 8.5 × 10 cm left-sided adrenal mass with a native

Abbreviations: CT, computed tomography; HPF, high-power field; HU, Hounsfield units; PAL, primary adrenal leiomyosarcoma; SMA, smooth muscle actin; ULN, upper limit of normal.

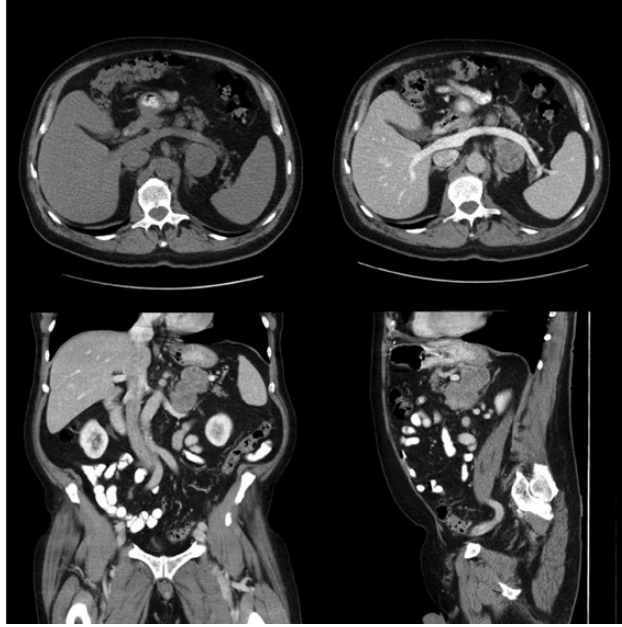


Figure 1. Computed tomography from subject #1, demonstrating a $4 \times 8.5 \times 10$ cm left-sided adrenal mass with a native attenuation of 32 Hounsfield units.

attenuation of 32 Hounsfield units (HU) (Fig. 1). There were no signs of invasion into the renal veins or infiltration into adjacent organs. The liver, pancreas, and spleen had an ordinary appearance and there were no signs of enlarged lymph nodes or skeletal metastases.

The patient had no clinical or biochemical signs of pheochromocytoma, Cushing syndrome or Conn syndrome. The following tumor markers in serum were within the normal reference range; chromogranin-A $49 \mu\text{g/L}$ (upper limit of normal [ULN] $102 \mu\text{g/L}$), placental alkaline phosphatase (PLAP) $< 30 \text{ mU/L}$ (ULN 100 mU/L), carcinoembryonic antigen (CEA) $< 0.5 \mu\text{g/L}$ (ULN $5.0 \mu\text{g/L}$), lactate dehydrogenase (LDH) $2.85 \mu\text{kat/L}$ (ULN $4.2 \mu\text{kat/L}$) and beta-human chorionic gonadotropin (beta-hCG) $< 5 \text{ U/L}$ (ULN 5 U/L). The primary differential diagnoses were lymphoma and a non-functioning adrenocortical carcinoma. The patient underwent open adrenalectomy, the tumor was located at the site of the left adrenal gland with no signs of invasion to adjacent organs. There were no postoperative complications and the patient was discharged 4 days after the surgery.

Gross pathological examination revealed a $9 \times 8 \times 4$ cm lobulated white-grey tumor. Microscopic examination revealed an infiltrative tumor with leiomyomatous differentiation with alternating areas of low- and high-grade cytological atypia, with the latter demonstrating pleomorphism (Fig. 2). Multiple necrotic foci were seen, comprising less than 50% of the total tumor area. Frequent mitotic figures were seen (10 per high-power field [HPF]; $0,1734 \text{ mm}^2$), including some atypical mitoses in the pleomorphic areas. The excision was histologically complete, with a narrow surgical margin measuring less than 1 mm. The tumor showed positive immunoreactivity for alpha smooth muscle actin (SMA), desmin, and h-caldesmon. The Ki-67 proliferation index was 40%. Based on these findings, the diagnosis of grade 3 PAL was confirmed, according to the Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) classification [4], with 3 points for tumor differentiation, 2 points for mitoses and 1 point for tumor necrosis.

Due to high proliferation grade and narrow margins, adjuvant chemotherapy was recommended after a discussion by a multidisciplinary team. However, in agreement with the patient, treatment with local conventional fractionated radiotherapy was instead initiated, with a total dose of 50 Gray units (Gy). Postoperatively, the patient has been followed every 3 to 6 months, without local recurrence. However, 31 months after the operation, metastases in the liver, sternum, mesentery, and gluteal muscle were discovered. After

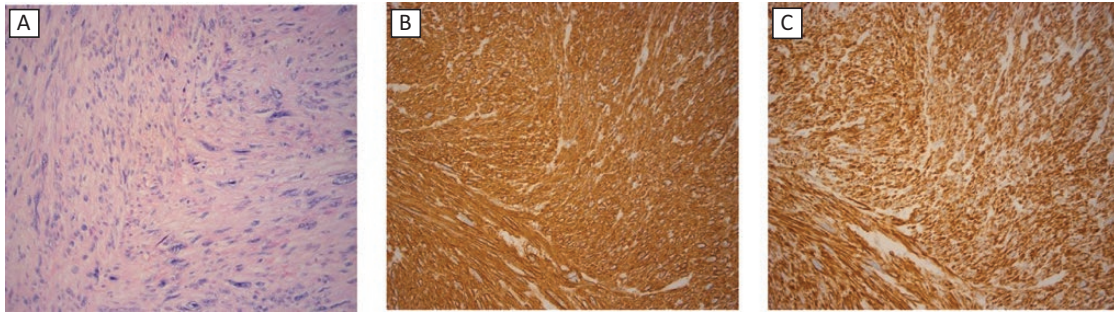


Figure 2. Microscopic features of primary adrenal leiomyosarcoma from subject #1. (A) Hematoxylin Eosin staining showcasing atypical spindle cells and pleomorphic cell nuclei; (B) Tumor cells staining positive for smooth muscle actin; and (C) Positive immunostaining for Desmin.

reassessment, the patient was again offered palliative chemotherapy but chose to decline it. Today, 48 months after the primary operation, the patient is still alive.

Subject #2

A 66-year-old man, with a history of type 2 diabetes, hyperlipidemia, and benign prostate hyperplasia, presented with macroscopic hematuria. Nephrolithiasis was suspected. CT-urography revealed no abnormalities in the urinary tract. Instead, a $7.5 \times 6 \times 4$ cm retroperitoneal tumor with a native attenuation of 38 HU was found at the right suprarenal pole (Fig. 3). Adrenal hormones were normal. An endoscopic ultrasound-guided fine-needle aspiration biopsy, on the premise of suspected lymphoma, revealed an area of necrosis and spindle cells with an immunophenotype with a positive reaction towards SMA, desmin, and CD163. Supplementary imaging showed no signs of metastasis. A soft tissue sarcoma was suspected, and the patient underwent an open adrenalectomy. Perioperatively, tumor invasion into the inferior vena cava was discovered; hence, a surgical resection and reconstruction was performed. Postoperatively, the patient developed renal failure due to renal ischemia. Consequently, he had a prolonged recovery time, being discharged 2 weeks postoperatively.

Gross pathological examination of the $12.0 \times 10.0 \times 6.0$ cm surgical specimen revealed a whitish, encapsulated tumor measuring $4.3 \times 6.7 \times 7.0$ cm (Fig. 4). The surgical margins were generally narrow, with a 2.5×2.5 cm area showing an exposed tumor capsule without covering tissue. Parts of adrenal tissue were also seen adjacent to the tumor. Histological examination showed an encapsulated tumor with both well-differentiated leiomyomatous areas and pleomorphic areas with strong nuclear pleomorphism and bizarre nuclei. Mitotic figures were frequent (17 per HPF), with atypical mitotic figures seen in the pleomorphic areas. Multiple necrotic foci were seen, constituting less than 50% of the tumor area. No growth outside the tumor capsule was seen, indicating a complete excision with a narrow margin. The adrenal parenchyma proper was negative for malignancy and separated from the tumor by a capsule. The tumor was positive for SMA, desmin, h-caldesmon, and CD163. The Ki-67 index was 30%. The findings were consistent with a grade 2 PAL, with 2 points for tumor differentiation, 2 points for mitoses and 1 point for tumor necrosis.

Two months postoperatively, metastases were discovered in the thoracic wall, right femur, left gluteus maximus muscle, and the right lateral vastus muscle. A multidisciplinary team did not recommend adjuvant therapy due to the presence of impaired renal function. Instead, the patient underwent surgical excision of the metastases in the chest wall and femur. Since then, further metastatic deposits have been discovered subcutaneously, in the lungs, skeletal muscle, and bone. Due to slowly progressing disease, treatment with trofosfamide 50 mg once daily was initiated 15 months postoperatively, increased to 50 mg

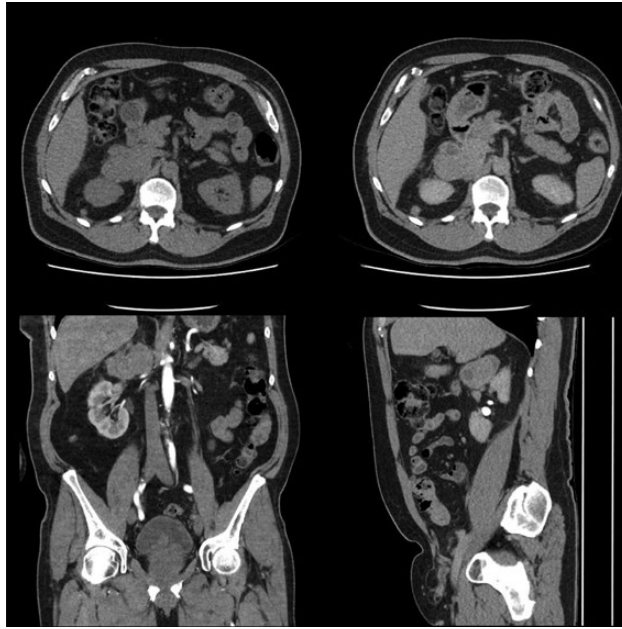


Figure 3. Computer tomography from subject #2, demonstrating a $7.5 \times 6 \times 4$ cm right-sided adrenal lesion, with a native attenuation of 38 Hounsfield units.

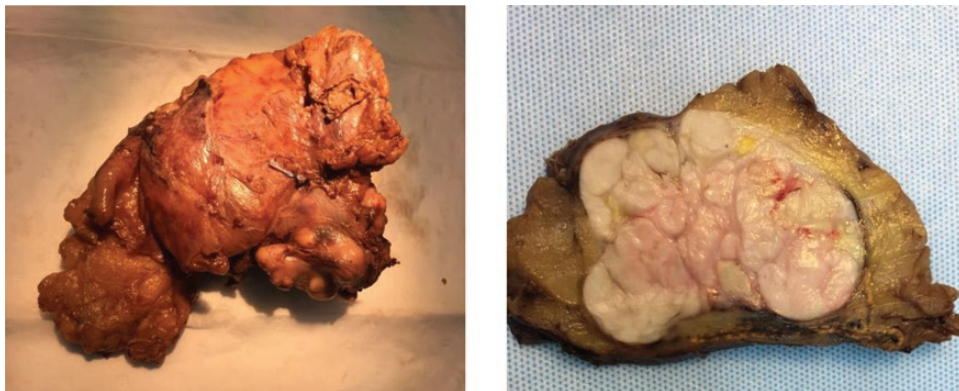


Figure 4. Macroscopic features of the tumor from subject #2, demonstrating a whitish, encapsulated tumour measuring $4.3 \times 6.7 \times 7.0$ cm.

twice daily after 19 months, but discontinued after 21 months due to worsening renal function. The patient is alive 23 months postoperatively.

Subject #3

A 58-year-old woman, with no previous medical history, presented with severe intermittent pain in the upper right abdomen. Cholelithiasis was suspected but an abdominal ultrasound revealed no abnormalities in the gallbladder. Instead, a malignant lesion in the liver was suspected. Subsequent CT of the abdomen revealed a $3.5 \times 5 \times 6$ cm left adrenal tumor with heterogeneous contrast enhancement (Fig. 5a, 5b, and 5c), together with multiple liver lesions, suspected to be metastases (Fig. 5d). A liver biopsy revealed spindle shaped cells that were positive for SMA, desmin, h-caldesmon, and vimentin, confirming the diagnosis of PAL. The Ki-67 index was 40%.

Due to multiple liver metastases, chemotherapy with dacarbazine and doxorubicin was initiated. After 4 months of treatment, disease progression was noted and second-line



Figure 5. Computer tomography from subject #3, showing a $3.5 \times 5 \times 6$ cm left-sided adrenal tumor and metastatic lesions in the liver.

treatment with gemcitabine and docetaxel were initiated instead. Today, 13 months after chemotherapy was initiated, the patient is alive with no signs of further tumor progression.

Discussion

PAL is a rare malignant tumor, representing only 0.1% to 0.2% of all retroperitoneal soft tissue sarcomas in adults [5]. Some 40 cases have been reported in the English-language literature to date [1-3, 5-36] (Table 1). The age at diagnosis ranges from 14 to 78 years, with 80% of the patients diagnosed after the age of 40 [1-3, 5-36]. PAL occurs both in males and females. The size of the tumor varies between 3 and 27 cm, with the vast majority (> 80%) being ≥ 4 cm in the largest diameter [1-3, 5-36]. Most patients present with unilateral PAL, and only 2 patients with bilateral PAL have been reported [11, 21]. PAL can be asymptomatic and discovered incidentally during imaging performed for reasons unrelated to the PAL itself, as was the case in all of our patients. The most common symptom at presentation is abdominal [1, 7, 9, 10, 18, 21, 23, 24, 26, 30, 32-36] or flank pain [2, 5, 12, 17, 19, 27, 31, 37]. Other symptoms include weight loss [9, 12, 19, 20, 27, 36] and peripheral edema due to tumor growth into the inferior vena cava [7, 16, 23]. Concomitant immunodeficiency has been reported in 2 cases [5, 10].

There are no distinct biochemical tests that are useful to identify and confirm PAL preoperatively. Adrenal hormones are consistently normal [1, 5, 16-18, 21, 22, 24, 29, 30, 33-36], and no specific tumor markers have been identified. Elevated concentration of neuron-specific enolase, which normalized postoperatively, was recently noted in one patient with PAL [17]. Neuron-specific enolase has not been reported elsewhere and further research on this potential biomarker is therefore warranted.

Imaging is important in patients with suspected malignant adrenal lesion for grading of the tumor, to determine the possibility of surgical resection, to discover metastases, and to estimate prognosis. PAL are most commonly discovered by using CT, typically showing lobulated mass with heterogeneous contrast enhancement [1, 5, 33-36]. Surprisingly, the radiological characteristics of PAL in terms of attenuation before and after injection of contrast have not been discussed previously. High native attenuation of 32 and 38 HU, respectively, was seen in both of our patients who had been investigated with unenhanced CT before

treatment. Other imaging modalities that may revealed PAL are abdominal ultrasound, demonstrating hypoechoic lesion that may be of either homogeneous or heterogeneous texture [9, 10, 22, 29, 30, 36, 38], and magnetic resonance imaging showing a mass with a low-signal intensity on T1-weighted images, high-signal intensity on T2-weighted images, heterogeneous contrast uptake and absence of loss-of-signal on an out-of-phase sequence [7, 16, 23, 39].

Currently, the diagnosis of PAL is based on histopathological and immunohistochemical findings, showing a neoplasm consisting of spindle cells that stain positively for one or more of the following smooth muscle cell markers; SMA [1, 2, 6-11, 16-18, 20, 21, 24-30, 32-34, 40], desmin [14-16, 19, 23, 25-28, 32], and vimentin [1, 5, 19, 20, 24, 26, 28, 33]. In

Table 1. A Summary of the Clinical Characteristics in Patients with Primary Adrenal Leiomyosarcoma Reported in the Literature

Author(s)	Year of Publication	Age (years) / Gender (M/F)	Size (cm) / Laterality (R/L)	Symptom(s)
Choi, Liu.	1981	50/F	16/L	-
Lack et al.	1991	49/M	11/R	Flank pain
Zetler et al.	1995	30/M	11/L	Immunodeficiency
Etten et al.	2001	73/F	27/R	Abdominal pain and vena cava syndrome
Matsui et al.	2002	61/F	-/R	Chest pain, vena cava thrombosis
Thamboo et al.	2003	68/F	12/R	Abdominal pain, fever, weight loss
Kato et al.	2004	59/M	10/L	Abdominal pain
Linos et al.	2004	14/F	3,5/R, 4/L	Immunodeficiency
Candanedo-González et al.	2005	59/F	16/L	Flank pain, weight loss
Wong et al.	2005	57/M	-/L	Groin pain, cyanosis, cold feet
Lee et al.	2006	49/M	3/L	-
Mohanty et al.	2007	47/F	10/L	Abdominal pain
Wang et al.	2007	64/F	13/R	Edema, hepatomegaly
Goto et al.	2008	73/F	8/R	Flank pain
Mencoboni et al.	2008	75/F	5/R	Epigastric pain
Tomasich et al.	2008	48/F	9/L	Flank pain, weight loss
Van Laarhoven et al.	2009	78/M	-/L	Weight loss, skeletal pain
Hamada et al.	2009	62/F	8/R, 4/L	Abdominal pain
Nanpo et al.	2009	78/F	10/L	Fever, nausea
Karaosmanoglu, Gee.	2010	63/M	-/R	Abdominal pain, edema
Kanthan et al.	2012	28/F	16.5/L	Abdominal pain
Shao et al.	2012	66/M	9.5/L	Nausea, abdominal fullness
Deshmukh et al.	2013	60/F	5.2/L	Abdominal pain
Lee et al.	2014	28/M	13.8/R	Flank pain, weight loss
Wei et al.	2014	57/F	7.7/L	Asymptomatic, routine medical examination
Gulpinar et al.	2014	48/M	8.6/R	Symptoms from the urinary tract
Ozturk.	2014	70/-	7.8/R	Abdominal pain
Alam et al.	2014	35/F	8.5/L	Flank pain
Bhalla et al.	2014	45/M	11/R	Abdominal pain
Nagaraj et al.	2015	61/M	16/L	Flank pain
Zhou et al.	2015	49/F	6/L	Abdominal pain, back pain
Quildrian et al.	2015	44/F	7.4/R	Abdominal pain
Onishi et al.	2016	34/M	5.2/R	Abdominal pain
Taniguchi et al.	2017	61/M	7/L	Abdominal pain
Mulani et al.	2018	50/M	8.1/L	Abdominal pain, weight loss
Doppalapudi et al.	2019	70/M	12/R	Edema, abdominal varices
Nerli et al.	2020	27/M	9//L	Back pain
Sakellariou et al.	2020	62/M	10/L	Asymptomatic, routine medical examination

addition to SMA and desmin, the tumors in our patients showed positive immunoreactivity for h-caldesmon, also a marker of smooth muscle cells, consistent with previous reports in patients with leiomyosarcomas of other origins [41]. The proliferation index Ki-67 was high (≥ 20) in all of our patients, which is in agreement with previous cases showing an index between 20% and 75% [1, 18, 30, 33, 34, 40].

As with other retroperitoneal leiomyosarcomas, PAL is a high-grade tumor with a significant risk of metastasis [42]. Delayed diagnosis, combined with high risk of metastasis, are the main reasons behind the overall poor prognosis. The longest reported survival in a patient treated with an adrenalectomy, without any known metastases, is 36 months [33]. The longest reported survival in a patient with a disseminated disease (liver and lymph nodes), treated with adrenalectomy, nephrectomy, and chemotherapy, is 53 months [19]. The most common sites for metastasis are the skeleton [2, 10, 20, 21, 40], liver [10, 12, 19, 32, 36, 40], lymph nodes [8, 19, 32, 34], and lungs [8, 36, 40]. Several cases have been reported where the tumor has invaded the inferior vena cava and caused a thrombosis [7, 10, 13, 16, 23, 30, 39]. In our patients, dissemination to liver, muscles, and bones occurred. Muscle metastases are in general rare, and usually derive from lung cancer, gastrointestinal, or urogenital tumors. One study found muscle metastases in roughly 5% of patients with sarcoma [43]. Two of our patients had muscle metastases, which have not been reported previously in patients with PAL.

The primary treatment for PAL is radical surgery with or without adjuvant chemotherapy or/and radiotherapy. The role of adjuvant therapy has not been evaluated in randomized trials due to the rarity of the disease. PAL should be assessed and managed by a multidisciplinary team. A thorough follow-up is important due to the high grade proliferating nature of the tumor where metastases can occur late, as seen in 1 of our patients and 5 other patients from previous reports [2, 12, 13, 21, 30].

Conclusions

PAL is a rare highly malignant tumor that is often diagnosed at an advanced stage. The most common symptoms at diagnosis are abdominal, flank, or back pain, weight loss, or peripheral edema due to occlusion of the inferior vena cava. On imaging, PAL almost always presents with characteristics compatible with malignant lesions, where the main differential diagnoses are adrenocortical carcinoma, metastasis, and lymphoma. The primary treatment is surgery, often with subsequent adjuvant chemotherapy and/or radiotherapy. Unfortunately, the overall prognosis for patients with PAL is, however, poor and the vast majority eventually develop a therapy-resistant and incurable metastatic disease.

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Additional Information

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Disclosure Summary: The authors have nothing to declare.

Data Availability: All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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