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Case Report

Next-Generation Sequencing: Key for Diagnosing Angiomyolipoma – A Case Report

José Revilla López[a] Rainer Enciso Chancahuana[b] Sayuri Meza Cruzado[b] Francisco Meléndez Ríos[b] Yashira L. Negrón Abril[c] Daniel Sumarriva[c] Timothy Samec[c] Yasser Sullcahuaman Allende[d] Ivan Chávez Passiuri[d] Luis Casanova Marquez[a] Carlos Carracedo Gonzáles[a]

[a]ALIADA Centro Oncológico, Lima, Peru; [b]Sociedad Científica San Fernando – UNMSM, Lima, Peru; [c]Caris Life Sciences, Phoenix, AZ, USA; [d]Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru

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Angiomyolipoma · *TSC2* · Retroperitoneal tumor · Next-generation sequencing

Abstract

Introduction: Renal angiomyolipomas (AMLs) are rare tumors categorized within the perivascular epithelioid cell tumor (PEComa) family, most of which are benign, except for epithelioid AMLs (EAML) with malignant potential. EAML develops sporadically or as part of the tuberous sclerosis complex (TSC), where mutations of the *TSC1/2* genes result in increased activation of the mammalian target of the rapamycin (*mTOR*) signaling pathway. ***Case Presentation:*** A 52-year-old female patient experienced dyspnea and abdominal pain, leading to the discovery of a retroperitoneal tumor confirmed by tomography. She was initially diagnosed with a retroperitoneal liposarcoma with lung metastasis. Following a first-line anthracycline-based chemotherapy, the patient achieved a complete clinical and tomographic response. Subsequent surgical resection of the primary tumor and a course of ifosfamide monotherapy yielded a 36-month progression-free survival to date. Comprehensive molecular profiling of the primary tumor by whole exome sequencing revealed pathogenic mutations in *TSC2* and the absence of amplifications in *MDM2* and *CDK4*, raising the need to consider a differential diagnosis in PEComas, and contemplate the potential use of *AKT/Pi3K/mTOR* pathway inhibitors. Pathological re-evaluation confirmed the diagnosis of a metastatic retroperitoneal AML with complete response and no evidence of disease. ***Conclusion:*** This case underscores the invaluable role of next-generation sequencing testing in the differential diagnosis of retroperitoneal tumors, as well as the ability to identify precise therapeutic targets for the treatment of rare soft tissue cancer types within the realm of precision medicine.

Correspondence to:
José Revilla López, oncologia@hndac.gob.pe

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Introduction

Soft tissue sarcoma (STS) comprises a diverse group of over 50 subtypes of rare mesenchymal tumors, representing less than 1% of adult cancers [1]. Among these STS subtypes, two noteworthy entities are retroperitoneal liposarcomas (LPS) and exophytic renal angiomyolipomas (AML). Both contain fatty components, although their clinical characteristics vary significantly. Retroperitoneal LPS, a rare and malignant tumor that originates in the retroperitoneal space, ranks as one of the more common types of STS, accounting for 15% of all cases [2]. LPS is divided into morphological variants such as well-differentiated LPS (WDLPS), dedifferentiated LPS (DDLPS), myxoid LPS, and pleomorphic LPS. These variants exhibit varying degrees of aggressiveness, with DDLPS and pleomorphic LPS showing a high metastatic potential [3]. Conversely, renal AML is a mostly benign mesenchymal neoplasm classified within the perivascular epithelioid cell tumor (PEComa) family [4]. AML has reported prevalence rates of approximately 440 cases per 100,000 people (0.44%) and females having higher rates than males (0.60% vs. 0.28%) [5]. AML typically occurs in the kidney and is known for their unique composition, featuring smooth muscle, adipocytes, and blood vessels; however, larger lesions may be exophytic from the kidney. While AML is typically a benign entity, the epithelioid AML (EAML) subtype tends to metastasize to the liver, lungs, and bones. It often affects individuals at a younger age, with an average age of 49.7 years and a predominantly female demographic [6].

In clinical practice, it is common for retroperitoneal LPS and exophytic AML to bear a striking resemblance, leading to occasional diagnostic challenges [7]. There are similarities in imaging due to large renal AML extending outside the kidney into the perinephric space. This case highlights the importance of their accurate differentiation as it significantly impacts patient prognosis and treatment strategies. With advancements in next-generation sequencing (NGS), our understanding of the intricate genetic landscape of STSs has expanded. DDLPS and WDLPS are often characterized by amplifications of the *MDM2* and *CDK4* genes, while PEComas, including AML, frequently exhibit mutations in the *TSC1* and *TSC2* genes [8, 9]. The primary objective of this report is to present a compelling case where NGS technology contributed to differentiating the diagnosis between AML and LPS, underscoring the clinical significance of an accurate diagnosis in guiding appropriate treatment strategies.

Case Report

A 49-year-old woman, without significant comorbidities or relevant medical, family, psycho-social, and surgical history, was admitted to the doctor's office with a 6-month history of non-specific upper respiratory symptoms. The patient's molecular test for COVID-19 yielded negative results, and smear tests for mycobacterium were also negative. Later, the patient presented with abdominal pain of progressive intensity (VAS 8/10 on a visual analog scale) and progressive dyspnea without requiring supplemental oxygen. At the time of presentation, the patient had had an ECOG Performance Status grade of 2, exhibited tachypnea, and had a large abdominal tumor that occupied the entire abdominal cavity with no peripheral lymphadenopathy. There were no clinical signs of tuberous sclerosis. Thoracoabdominopelvic multislice spiral computed tomography with contrast showed an abdominal tumor measuring 22 × 13 × 14 cm in the intraperitoneal and retroperitoneal compartments (Fig. 1a). The patient also showed multiple metastatic nodules in both lung fields, the largest of which was 2 cm (Fig. 1b). Hematology, blood biochemistry, kidney, and liver function, LDH, and tumor marker tests revealed no abnormalities. An initial histological diagnosis of LPS was

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established upon percutaneous biopsy of the bulky retroperitoneal mass. The final diagnosis confirmed a stage IV, G1 primary retroperitoneal WDLPS with multiple bilateral lung metastases. In July 2020, the patient initiated first-line systemic treatment based on monotherapy with anthracyclines (Adriamycin 75 mg/m^2) for 6 courses. Tomographic re-evaluation studies revealed a neoformative-like lesion with a predominantly fatty composition (9.3 × 7.6 × 7.0 cm), located adjacent to the anterior border of the kidney, and diffusely distributed pulmonary pseudo-nodules with decrease in size and number, indicating partial response by RECIST 1.1 criteria. It should be emphasized that partial clinical response was observed from the first course of monotherapy with anthracyclines.

In February 2021, an exploratory laparotomy was performed which showed a tumor originating in the anterior perinephric space that infiltrated the upper pole of the left kidney. A complete removal of the tumor was performed through a left nephrectomy procedure. The pathological examination unveiled a WDLPS tumor, solid and necrotic in nature, measuring 15 × 8 × 7 cm. The tumor exhibited a fatty composition and extended to encompass the renal capsule, renal parenchyma, and renal sinus, without encroaching upon the renal pelvis. Both microscopic and macroscopic assessments confirmed clear, uninvolved margins (R0 oncological surgery) (Fig. 1c, d).

Given that the patient reached the maximum dose of anthracyclines (cumulative dose 420 mg/m^2) and achieved a partial response (RECIST 1.1), a second line of therapy based on ifosfamide monotherapy (1.8 g/m^2/d, day 1–3) was given from March 2021 to July 2023. The patient displayed good tolerance and achieved a complete overall response in August 2021. Grade 1 proteinuria without clinical significance was the only adverse event reported. The patient has undergone semiannual monitoring via computed tomography imaging, consistently exhibiting no evidence of disease (NED) progression (Fig. 1e, f). As of the current date, the patient has achieved disease-free survival of 36 months (Fig. 2a, b).

Comprehensive molecular profiling of the tumor was performed to identify actionable biomarkers and additional therapeutic options. NGS identified the presence of a pathogenic mutation in *TSC2* (40% Variant Allele Frequency), a genetic alteration typically associated with the development of AML and other types of PEComas. This analysis also ruled out the presence of amplifications in the *MDM2* and *CDK4* genes, raising the need to expand the differential diagnosis to neoplasms of the PEComas group and implying the possibility of considering administering inhibitors of the *AKT*/*Pi3K*/mammalian target of the rapamycin (*mTOR*) pathway, if necessary, in the case of recurrence.

Given the broad differential diagnosis, a review of biopsy slides and surgical specimens was requested. Histopathological re-evaluation of the surgical tumor sample demonstrated positivity for melan-A and HMB 45 (Fig. 3a–c). These results confirmed the diagnosis of AML. In summary, the current patient's status is ECOG 0, NED, and under active observation. The diagnosis was modified from retroperitoneal LPS to renal AML.

Discussion

This case highlights the utility of molecular platform on defining intricate diagnostics involving adipocytic tumors, specifically AML and LPS. *TSC2* mutation and the absence of *MDM2* and *CDK4* amplification refocused the diagnosis toward AML. Several factors contributed to this diagnostic challenge, including the predominance of fatty tissue observed in the core biopsy and the initial clinical impression that the neoplasm was retroperitoneal rather than renal in origin. The clinical presentation, featuring a retroperitoneal fatty tumor with signs of lung metastasis, initially suggested LPS. In this case, the AML's extensive adipose content made it increasingly difficult for the muscular and vascular components to be identified. This tissue affected the result of the Core Biopsy report and was further convoluted

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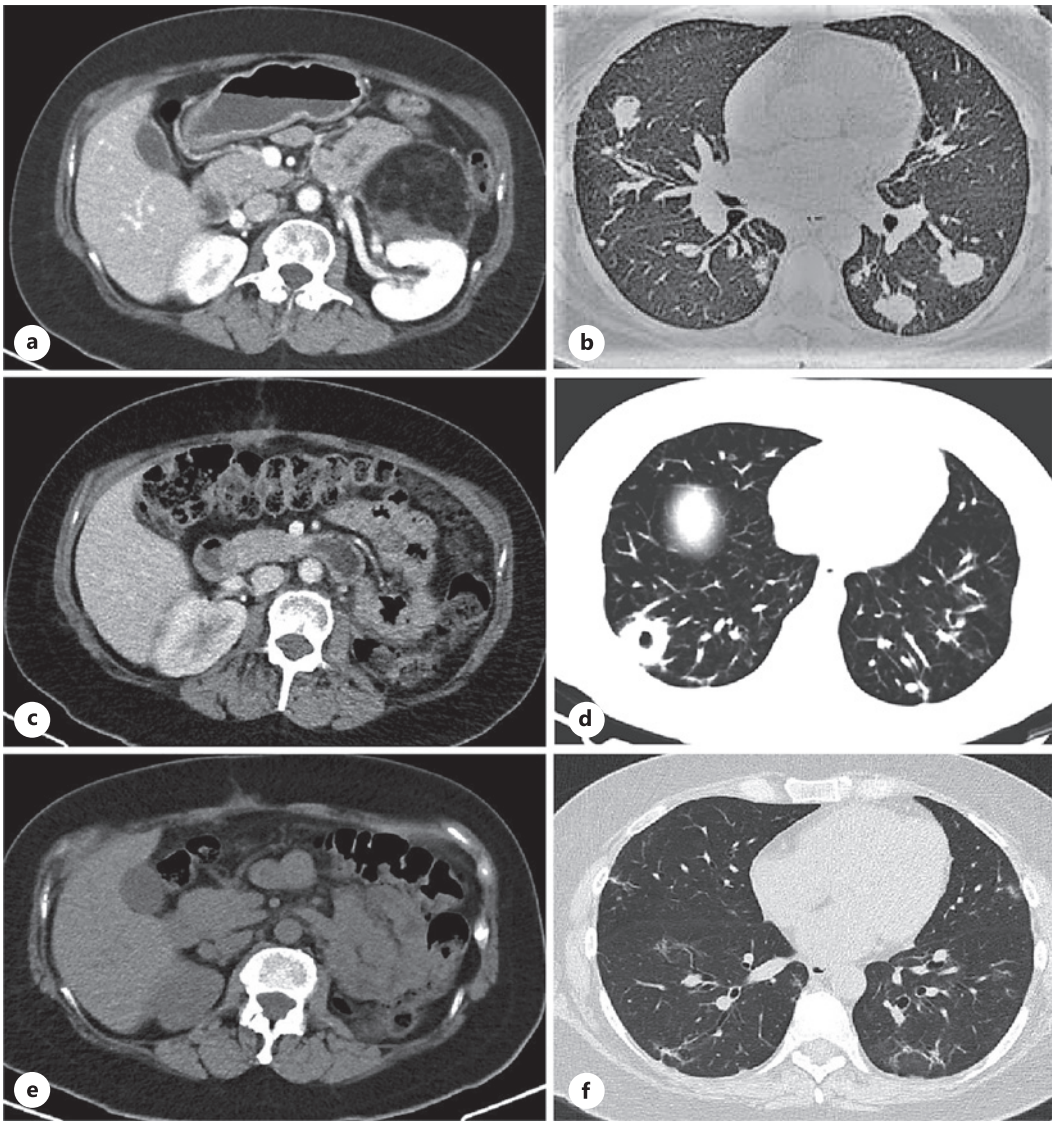

Fig. 1. Computed tomography (CT) images at diagnosis (**a**, **b**) and post-surgery (**c–f**). **a** Abdominal CT scan at diagnosis showing a left intra-abdominal tumor measuring 22 × 12 × 14 cm, located intraperitoneally and retroperitoneally. It shows a fatty component with soft tissue density. **b** Chest CT scan at diagnosis showing multiple rounded nodules of varying sizes with well-defined edges in both lung fields, with the largest nodule measuring 35 mm density of 50 HU. **c** Post-surgical CT scan of the pelvis, taken 41 days after surgery, showing no evidence of neoformative lesions, lymphadenopathy in the iliac chains, or free fluid, with no significant changes compared to the previous study. **d** Post-surgical CT scan of the chest, taken 41 days after surgery, reveals an enlargement of pseudonodular lesions in both lungs and the emergence of a new cavitated nodule in the right lateral basal segment. **e** Post-surgical CT scan of the pelvis without contrast, taken 180 days after surgery, showing no evidence of neoformative lesions or lymphadenopathy in the iliac chains, with no significant changes compared to the previous study. **f** Post-surgical CT scan of the chest without contrast, taken 180 days after surgery, showing a stable disease with no progression of pseudo-nodules in both lungs compared to the previous study. No cavitated lesions are observed, and mediastinal lymphadenopathy appears to be reactive due to its stable evolution.

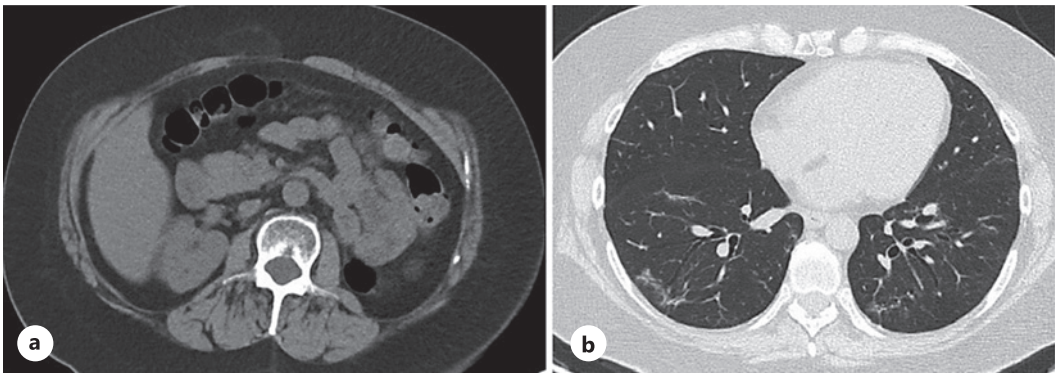

Fig. 2. CT scan images from the patient's latest re-evaluation. **a** Abdominal CT scan showing no evidence of locoregional recurrence, bone lesions, retroperitoneal adenopathy, or free fluid. **b** Chest CT scan showing stable pseudonodular lesions in both lungs, with no cavitated lesions, indicative of sequelae. Ganglia in the aortopulmonary window and in the pretracheal retrocaval space show a stationary course, indicative of sequelae. CT, computed tomography.

by a limited tissue sample. The size of the tumor (22 cm) and the strong likelihood of distant metastasis contraindicated the diagnosis of AML. However, giant AML tumors, exceeding 20 cm, have been reported [10]. AML is characterized by spindle-shaped smooth muscle cells expressing smooth muscle actin and melanocytic markers, particularly melan-A and HMB 45, which serve as differential markers for AML, aiding in distinguishing it from other primary epithelial, primary mesenchymal, and secondary tumors [3]. The surgical specimen's necrotic tissue prompted immunohistochemistry in a scant muscle area to confirm the diagnosis of AML. Notably, among AML subtypes, only the epithelioid variant is associated with metastatic potential [4].

Surgical management remains essential, particularly for larger AML tumors, given the associated symptoms like dyspnea and the heightened risk of intratumoral hemorrhage. Despite the initial AML diagnosis, a surgical excision approach is required, albeit adopting a more conservative strategy [11]. To complicate matters, the absence of a pathological sample from the pulmonary metastatic component presents yet another challenge in confirming the tumor origin as AML. Obtaining a biopsy of the lung nodules is essential to reach a consensus on the most appropriate treatment approach but may present further patient surgical and psychological burden. In addition, our patient dealt with the psychological impact resulting from diagnostic changes. The medical act extends beyond identifying and managing diseases, encompassing a comprehensive approach to patient care. This highlights the challenge of treating oncologists in effectively communicating and supporting patients throughout the diagnostic process; however, precision medicine may aid in this effort through specific molecular diagnostics.

Precision medicine goes beyond clinical and histopathological criteria. It requires using tools that guide diagnosis and specific therapy against the molecular genetic profile of the tumor. Tumor DNA studies utilizing NGS technology have proven indispensable in establishing molecular subtypes and selecting tailored target therapies. This approach is grounded in the detection of oncogenic mutations and their impact on molecular pathways, serving as the foundation for drug selection. NGS also contributes significantly to the diagnosis of soft tissue and bone tumors, providing insights into the pathogenesis of these rare tumors and enabling a more detailed genetic classification [12]. Notably, diagnostic difficulties between AML and LPS have arisen from their shared high adipose content, requiring confirmation through immunohistochemistry in multiple case reports

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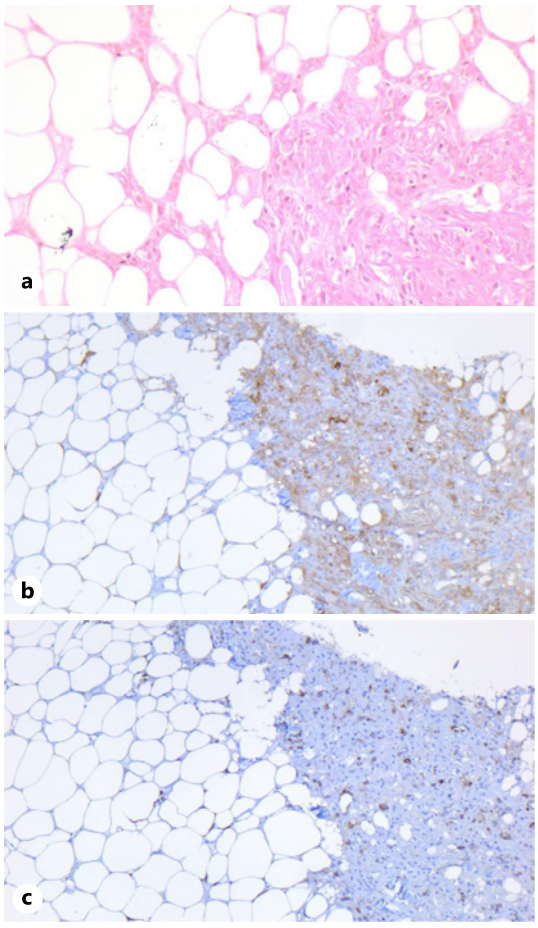

Fig. 3. Histological images of the resected tumor. **a** Representative hematoxylin and eosin image displaying the tumor at ×40 magnification. **b**, **c** Representative images, taken at ×10 magnification, of the tumor evidencing the expression of melan-A (**b**) and HMB 45 (**c**), consistent with an AML.

[7, 13]. Importantly, there is limited documented use of NGS as a diagnostic support in AML [14].

In this case, the insights derived from NGS studies played a pivotal role not only for a differential diagnosis but also for considering potential treatment options, such as selective inhibitors targeting the *mTOR/Akt/PI3CA* pathway. The presence of a *TSC2* mutation points toward the therapeutic advantage of *mTOR* inhibitors such as everolimus and temsirolimus over alternative regimens, including antiangiogenic tyrosine kinase inhibitors, gemcitabine, and anthracycline-based treatments [15].

Conclusion

The differential diagnosis of retroperitoneal sarcomas is always an oncological challenge and must be based on a clinical-radiological-pathological correlation. If necessary, it is feasible to implement technologies such as NGS as the definitive diagnostic tool, though this may have implications regarding the medical-surgical approach and patient prognosis. In the case presented, NGS identified a mutation in the *TCS2* gene and the absence of *MDM2* and *CDK4* amplification, suggestive of a neoplasia of the PEComa lineage. Histopathological confirmation concluded that AML was the definitive diagnosis and was the origin of pulmonary metastasis. Radiological evidence by RECIST 1.1 indicates complete response to systemic treatment, moving the patient to observation, maintaining

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29 months NED to date. Accurate diagnosis of retroperitoneal sarcomas requires a multidisciplinary approach, integrating clinical, radiological, and molecular data. This case demonstrates the pivotal role of precision medicine and molecular profiling in refining differential diagnoses, impacting treatment decisions, and, subsequently, influencing patient prognosis. It underscores the evolving landscape of cancer diagnosis and treatment, propelled by genomic insights.

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Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent for publication of this case report and any accompanying images has been obtained from the patient. All identifying information has been removed to preserve confidentiality. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000542960).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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Data Availability Statement

All data generated or analyzed during this study are comprehensively documented within this article. Further inquiries can be directed to the corresponding author.

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