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ELOC-mutated renal cell carcinoma: "Unexpected occurrence in a younger adult"

Akansha Deshwal, Himani Kumar, Daniel Jones, Anil Parwani

ABSTRACT

ELOC-mutated renal cell carcinoma (RCC) is a rare, molecularly defined RCC described in the 2022 WHO classification of genitourinary tumors. These tumors mostly affect middle-aged to elderly males, with approximately 30 cases reported in the English literature to date. A definitive diagnosis requires the identification of characteristic molecular alterations in conjunction with histopathological findings. Herein, we report an unusual case of ELOC-mutated RCC in a young male, identified by a mutation in the hotspot codon and a 1-copy loss of chromosome 8 sequences consistent with biallelic ELOC dysregulation. Due to its close resemblance to clear cell RCC, it is frequently misclassified, underscoring the importance of molecular characterization for accurate diagnosis. This case report aims to bridge the knowledge gap for this rare entity by focusing on clinical presentation, multimodal diagnostic approach, differential diagnosis, and prognostic considerations.

Keywords: Clear cell, ELOC-mutated RCC, TCEB-1

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INTRODUCTION

The ever-evolving classification of kidney tumors has gained new recognition after the introduction of molecularly defined renal cell carcinomas (RCCs). Renal cell carcinomas with clear cell morphology showed a wide clinical spectrum, ranging from indolent tumors such as clear cell papillary RCC (CCPRCC) to aggressive subtypes like MITF-related RCC [1]. Within the spectrum of indolent tumors lies the rare ELOC-mutated RCC, formerly known as TCEB1-mutated RCC, which is recognized as a distinct entity in the WHO classification, 2022 [1, 2]. ELOC-mutated RCC accounts for 0.5% to 5% of clear cell RCC [3] and shares morphologic homology with RCC with leiomyomatous stroma (RCCLMS) [4], Von Hippel-Lindau (VHL)-mutated CCPRCC, and sporadic and hereditary TSC-associated RCC [5].

Among molecularly defined RCCs, ELOC-mutated RCCs are known as next-generation sequencing (NGS) identifiable tumors and exclusively recognized by the classic gene alteration, making it an essential diagnostic criterion [6]. These tumors were first described by Sato et al. in 2013, and subsequently, additional cases have been added [1]. However, to the best of our knowledge, fewer than 30 have been documented in elderly patients; its occurrence in younger individuals is exceedingly rare. Thus, we aim to present a case of incidental ELOC-mutated RCC in a young male, underscoring its clinicopathologic findings, histologic mimickers, and molecular insights into this rare and diagnostically challenging entity.

CASE REPORT

A 35-year-old male patient was detected with an incidental renal mass during evaluation for an abnormal liver function test during his annual physical examination. A right upper quadrant ultrasound was performed, which

showed a normal-sized right kidney, with a 2.5 × 2.3 × 1.9 cm solid mass within the lower pole demonstrating increased echogenicity relative to the adjacent cortex. The liver was mildly echogenic, reflecting a possible hepatic steatosis. A follow-up contrast-enhanced magnetic resonance imaging (MRI) was recommended for further evaluation of the renal mass. Magnetic resonance imaging urography revealed a mass arising from the lower pole of the right kidney laterally, with a heterogeneous T1 intermediate T2 signal mass measuring 2.8 × 2.3 × 2.1 cm, which showed a solid enhancement following contrast administration consistent with a renal cell neoplasm (Bosniak type IV). There were no additional lesions or hydronephrosis, and no perinephric edema. The right renal vein was patent.

We received a partial nephrectomy specimen, which showed a tan-orange, soft, well-circumscribed nodule measuring 2.4 cm abutting the renal capsule. On histopathological examination, the tumor was encapsulated with tubulopapillary architecture. The lesion was characterized by thick, intersecting fibromuscular bands that gave a nodular growth pattern. The tumor cells had abundant clear cytoplasm, distinct cell borders, and hyperchromatic nuclei with irregular nuclear membranes (Figure 1).

Immunohistochemistry showed tumor cell positivity for CD10, PAX8, alpha methylacyl CoA racemase (AMACR), AE1/AE3, and focal KRT7, with negativity for TFE3 and CD117 (Figure 2). Based on the above findings, a diagnosis of renal cell carcinoma with clear cell features was made. Next generation sequencing (NGS) was carried out using a 540-gene bait-probe-based assay on an Illumina 550 NextSeq with 300-cycle reagent kits (Illumina, San Diego, CA). The reagents used were IDT xGen gene capture probes (Integrated DNA Technologies, Inc., Coralville, IA) and KAPA HyperPrep Kit (Roche, Indianapolis, IN). Next generation sequencing detected a missense mutation at tyrosine 79 (Y79c), a hotspot codon of VHL-binding domain [7], representing a characteristic molecular signature mutation of ELOC-mutated RCC (Figure 3A). An EP300 inactivating variant was also detected, without mutations in VHL or other RCC-associated genes, and no TFE3 or TFEB fusions were identified [8]. Copy number analysis revealed loss of chromosome 8 sequences, including ELOC, without loss of the 3p chromosome (3p deletion is more characteristic of clear cell RCC, which helps differentiate from ELOC-mutated RCC). These observations were concordant with fluorescence in situ hybridization (FISH) results, which also did not show 3p deletion.

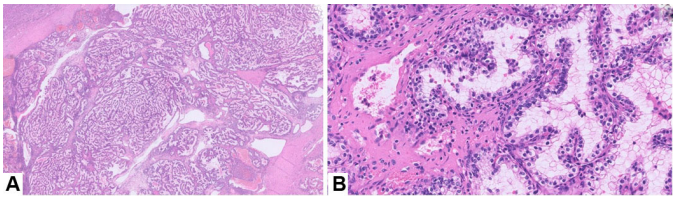

Figure 1: Histopathological features of ELOC-mutated RCC. (A) Low-power view shows an encapsulated tumor with tubulopapillary architecture separated by thick intersecting fibromuscular bands (1 × 10 magnification). (B) High power view shows tumor cells are polyhedral with abundant clear cytoplasm, hyperchromatic nuclei, and irregular nuclear membrane (20 × 10 magnification).

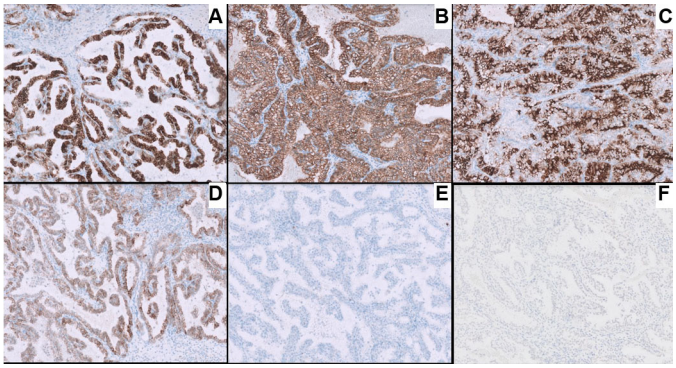

Figure 2: (A) Immunohistochemical panel for ELOC-mutated RCC (20 × 10 magnification). Immunohistochemistry for KRT 7 shows diffuse staining of the tumor cells. (B) Immunohistochemistry for CAIX shows a box-shaped pattern of positivity. (C) Immunohistochemistry for CD10 shows diffuse staining of the tumor cells. (D) Immunohistochemistry for AMACR shows diffuse staining of the tumor cells. (E) Immunohistochemistry for CD117 shows negative expression in tumor cells. (F) Immunohistochemistry for TFE3 shows negative expression in tumor cells.

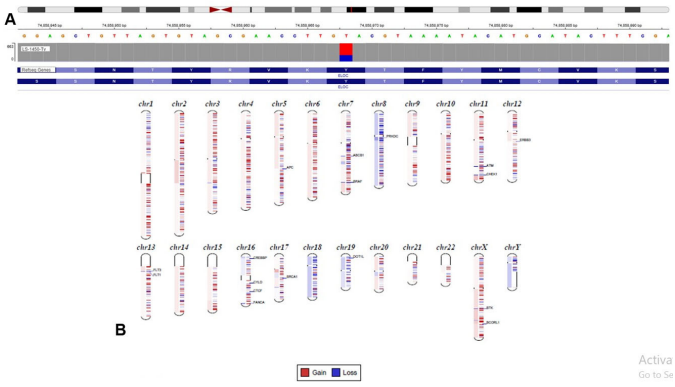

Figure 3: Molecular findings of ELOC-mutated RCC. (A) ELOC p.Y79C mutation was detected at 36.4% variant allele fraction by a comprehensive NGS panel (IGV viewer). (B) Copy number analysis using CNVkit software on NGS data revealed a 1-copy loss of chromosome 8 sequences, including ELOC, consistent with biallelic ELOC dysregulation.

DISCUSSION

Since the advent and implementation of molecular techniques, RCCs with clear cell change that appear morphologically similar have been recognized as molecularly defined entities, harboring driver mutations in TSC1, TSC2, MTOR, and VHL genes. More recently, RCC with ELOC mutations emerged as a molecularly defined RCC with characteristic histomorphology and molecular alterations. ELOC-mutated RCC was first

reported by Sato et al. through molecular analysis of 106 clear cell RCCs, which identified 5 cases lacking the classic 3p deletion and/or VHL mutations. Instead, these tumors showed mutations in ELOC (formerly referred to as TCEB1) and/or showed deletion/loss of heterozygosity at the ELOC locus on chromosome 8 [1]. Since this initial discovery, a wider range of ELOC alterations has been described.

The ELOC gene, located at chromosome 8q21, encodes Elongin C, a subunit of the transcription factor B (SIII) complex and a component of the VHL complex. When mutated, the ELOC protein alters the association of HIF (hypoxia-inducing factor B) with the VHL complex, preventing its degradation by ubiquitination [6]. The stabilized HIF translocate into the nucleus, resulting in the overexpression of HIF target genes involved in dedifferentiation, VEGF production, and cell migration, facilitating tumorigenesis as well as metastatic processes [8]. Molecularly, these tumors harbor unique genetic changes in the ELOC mutation sites at the pVHL binding domain: A100, I95, and Y79 [9]. In our case, a Y79C mutation (and an EP300 inactivating variant) with no loss of chromosome 3p was identified, concurrent with previous studies suggesting that these aberrations are mutually exclusive [10].

ELOC-mutated RCC is an extremely rare entity. However, the limited literature suggests that it typically occurs in middle-aged and elderly male patients, with a male-to-female ratio of 22:1. The usual age of presentation is 38–77 years, with a majority of patients aged approximately 50 years old, as compared to translocation-related RCCs, and may present incidentally [4, 11]. In our case, the tumor was detected incidentally at a relatively early age compared to previous literature.

Histopathologically, the tumor shows predominance of clear cells with voluminous cytoplasm with unique histological findings, such as smooth muscle predominant fibrous pseudocapsule and fibromuscular bands more prominent at the periphery of the tumor, giving the tumor nodular to branched acinous or tubular architecture, and infrequently, focal papillary formations may be noted [4, 12]. However, due to clear cell morphology, these tumors share morphological homology with existing and novel entities like clear cell renal cell carcinoma (ccRCC), RCCs with fibromuscular stroma (RCCFMS), and clear cell papillary renal cell tumor (CCPRCT) [10] and are unanimously differentiated by subtle histopathological findings and two distinguished immunohistochemical stains, i.e., CAIX and KRT7. ELOC-mutated RCC bears a distinct immunohistochemical (IHC) profile characterized by a combination of clear-cell and non-clear-cell markers– box-shaped carbonic anhydrase IX labeling (CA IX), CD10+/KRT7+, AMACR+, epithelial membrane antigen (EMA+/–) (Figure 2, Table 1) [11]. In contrast, ccRCC exhibits diffuse membranous CAIX labeling, KRT7 focal/–, while CCPRCT shows cup shaped CAIX labeling, KRT7+, CD10–, EMA+/–, AMACR–, and reverse nuclear polarity with subnuclear vacuolation (Table 1) [12]. The fibromyomatous stroma seen in ELOC-mutated RCC often shows positivity for SMA and desmin.

At molecular level, ELOC-mutated RCC display distinct wild-type VHL and somatic mutations in the TCEB1 gene, as well as loss of the alternate allele (8q21) [1], which contrasts with the biallelic inactivation of the VHL gene found in ccRCC (Table 1) [13].

Nevertheless, molecular characterization of ELOC mutation is of paramount importance in histologically indistinguishable RCCFMS caused by mutations of the mTOR pathway [4, 6, 14], but before the molecular era, the analogous tumors were blanketed under the same category [15]. However, in previous studies, biallelic inactivation of ELOC and TSC/MTOR mutations were found to be mutually exclusive of each other, supporting the notion that RCCFMS and ELOC-mutated RCCs are distinct entities [10].

Thus, a definitive diagnosis of ELOC-mutated RCC can exclusively be determined by complex molecular analysis [10], i.e., absence of 3p deletion and/or VHL mutations and biallelic ELOC deletion (loss of both copies of the ELOC gene), while monoallelic deletion (loss of a single copy of the ELOC gene) with clear cell morphology should be diagnosed as ccRCC [10]. However, by convention, renal tumors with clear cell morphology in the absence of molecular confirmation can be designated as "KRT7 positive ccRCCs with prominent fibromuscular septations," and differentials may be suggested [16].

However, even in optimally and radically resected tumors, accurately recognizing this entity could avert unnecessary adjuvant therapies typically used for ccRCC [6]. Unlike metastatic ccRCC, which often requires VEGFR tyrosine kinase inhibitors (TKIs), mTOR inhibitors, or immune checkpoint inhibitors, ELOC-mutated RCC is generally indolent, and surgery alone is usually sufficient for localized disease [17]. Molecularly, Hakimi et al. found that ELOC-mutated RCCs lack mutations in PBRM1, SETD2, and BAP1, as seen in more aggressive, VHL-inactivated RCCs [11].

Although ELOC-mutated RCCs are rare variants, they are known to have indolent behavior and are not clinically challenging, as the surgical resection is often curative. In the recent largest institutional series of 1209 RCCs, ELOC-mutated RCC (11/13) demonstrated a favorable overall and progression-free survival as compared to the stage and grade-matched VHL-null clear cell RCC. However, occasional ELOC-RCC (2/13) with solid alveolar pattern, necrosis, copy number variations, and extra monoallelic VHL copy loss correlated with high-stage and aggressive behavior [18]. A similar observation was made by diNatale et al., in which most of the tumors (4/5) were staged higher due to the presence of high-grade features like pleomorphism, prominent nucleoli, and necrosis, and clinically also found to have distant metastasis [8]. Although, due to rarity, there is no consensus on follow-up guidelines for ELOC-mutated RCC, the presence of high-grade, aggressive tumors in the literature underscores the importance of long-term surveillance even when low risk is anticipated [19].

Table 1: Comparison of ELOC-mutated RCC, ccRCC, and CCPRCT [1, 4, 9, 13]

Salient features	ELOC-mutated RCC	Clear cell RCC (ccRCC)	Clear cell papillary renal cell tumor (CCPRCT)
1. Histopathology	Clear cell morphology may mimic ccRCC or CCPRCT	Classic clear cell morphology	Papillary architecture; reverse nuclear polarity; subnuclear vacuolations
2. Immunohistochemical expression			
- CA-IX	Box-shaped pattern	Diffuse membranous labeling	Cup-shaped pattern (classic)
- KRT7	Positive	Focal or negative	Positive
- CD10	Positive	Variable	Often negative
- EMA	Variable	Positive	Variable
- AMACR	Strong	Usually, negative	Negative or weak
3. Molecular analysis			
- VHL status	Wild-type VHL; no VHL inactivation	Biallelic inactivation of VHL	Wild-type VHL
- ELOC gene mutation	Somatic ELOC mutation (most often p.Tyr79Cys), with loss of alternate allele (8q21) or biallelic ELOC gene dysregulation/ deletion (mutation plus deletion or double deletion).	Not detected or occasional monoallelic deletion of ELOC gene.	Not detected
- 3p deletion	Not detected	Detected	Not detected
Key differentiating features	Box-shaped CA-IX, KRT7+/ CD10+, strong AMACR ELOC mutation	Diffuse CA-IX, KRT7−/ EMA+ VHL inactivation, 3p deletion	Cup-shaped CA-IX, KRT7+, AMACR− Reverse nuclear polarity, subnuclear vacuoles

Glossary: Biallelic dysregulation/deletion—loss of both copies of gene; Monoallelic deletion—loss of a single copy of gene
Abbreviations: ccRCC: clear cell renal cell carcinoma; CCPRCT: clear cell papillary renal cell tumor; VHL: Von Hippel-Lindau; AMACR: alpha methylacyl CoA racemase; CA-IX: Carbonic anhydrase IX; EMA: epithelial membrane antigen; CD: Cluster of differentiation; KRT: Keratin

Thus, heterogeneous clinical spectrum, limited available literature, lack of follow-up guidelines, and gap in molecular targeted therapies for ELOC-mutated RCC underscores the importance of larger pooled case series and evidence-based studies to unfold the clinical outcome and biological behavior of this rare entity to guide future targeted therapies.

CONCLUSION

ELOC-mutated RCC should be considered even in young age groups, as it differs considerably from ccRCC in clinical behavior, prognosis, and treatment strategies. For renal tumors with clear cell morphology—a combined multimodal diagnostic approach including histopathology, IHC, and molecular analysis should be employed for accurate disease characterization. Importantly, the presence of the signature ELOC mutation remains the essential criterion for diagnosis.

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Author Contributions

Akansha Deshwal – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Himani Kumar – Design of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Daniel Jones – Conception of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Anil Parwani – Conception of the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

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Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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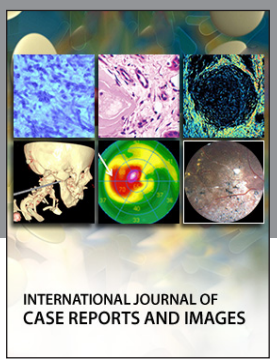

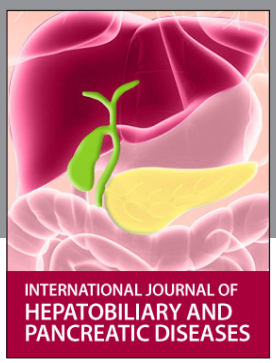

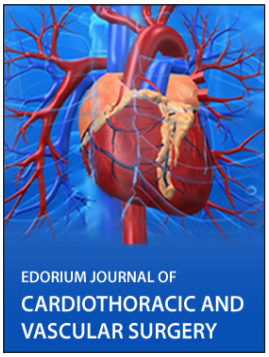

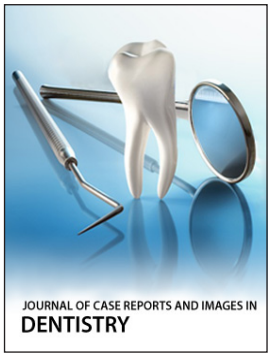

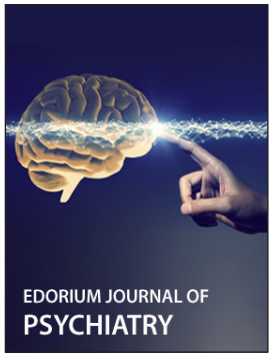

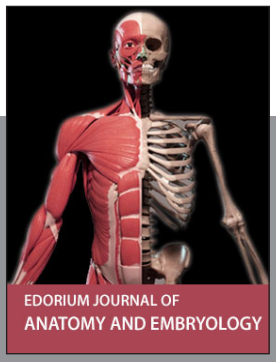

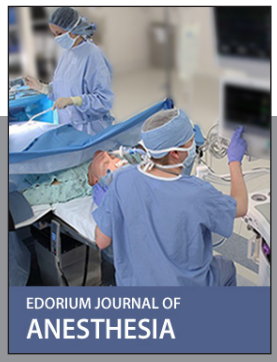

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