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Case Report

Radiologic and clinicopathologic features of eosinophilic solid and cystic renal cell carcinoma: report of two cases and review of literature

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Abstract: Eosinophilic Solid and Cystic Renal Cell Carcinoma (ESC RCC) is a rare entity described in the latest WHO Classification of Urinary and Male Genital Tumours (2022 edition). It is a neoplasm that occurs most often in a sporadic setting, with no association with tuberous sclerosis complex (TSC). It typically presents as a well demarcated, non-encapsulated lesion, with solid and cystic architecture, composed of cells with voluminous eosinophilic cytoplasm and cytoplasmic stippling. Tumor cells are at least focally immunohistochemically (IHC) reactive for CK20. CD10 and Cathepsin K are positive in most cases. Consistent somatic mutually exclusive mutations in the TSC1 and TSC2 genes are detected in ESC RCC. We describe two ESC RCC cases diagnosed at our institution. Both cases occurred in female patients, ages of 33 and 64, respectively. Both patients had no evidence of TSC and both lesions were found incidentally, by imaging studies, at an early stage. Macroscopic and microscopic findings in both neoplasms were classic. One case was analyzed by molecular testing and TSC2 gene mutation was detected. Both cases had focal positivity of CD10 and Cathepsin K by IHC. Both tumors were stage pT1a at diagnosis and the patients remained free of disease after resection. It has been proposed that TSC1/2 can be a molecular marker for ESC RCC and be used to expand the morphologic spectrum of ESC RCC. As a novel rare subtype of renal cell carcinoma, with very limited data on molecular evaluation, it is useful to document these newly diagnosed ESC RCC cases.

Keywords: Eosinophilic Solid and Cystic Renal Cell Carcinoma, radiography, morphology, immunohistochemistry, molecular study, TSC1, TSC2

Introduction

Eosinophilic Solid and Cystic Renal Cell Carcinoma (ESC RCC) is a novel entity that was included in the latest WHO Classification of Urinary and Male Genital Tumours (2022) [1]. This entity was originally recognized as a rare neoplasm with unique morphology seen only in patients with tuberous sclerosis complex (TSC) [2-4]. Later, it was found to occur more commonly in a sporadic setting in patients with no clinical findings of TSC [5, 6]. The incidence of ESC RCC is estimated to be around 0.2% [7]. This new entity demonstrates not only distinct clinical and morphologic features, but also immunohistochemical and molecular characteristics. The majority of cases are low-stage with indolent behavior. To date, rare metastatic ESC RCC cases have been reported [8-10]. ESC RCC has an extreme female predominance [1, 5] with a wide age range [5]. Sporadic ESC RCC in teenagers was documented [10, 11]. ESC RCC typically is a well-demarcated non-encapsulated lesion with solid and cystic architecture upon gross examination. Macrocysts are considered to be a significant gross feature [5]. Microscopically, bland neoplastic cells with voluminous eosinophilic cytoplasm and fine or coarse cytoplasmic stippling (basophilic or eosinophilic granularity, which is rough endoplasmic reticulum aggregation) are the most helpful histopathologic findings [7]. Diffuse or focal immunoreactivity for CK20 is found in the majority of ESC RCC. CD10 and Cathepsin K are also reported to be positive in most cases [7, 12]. CK7 is usually negative or very focally posi-

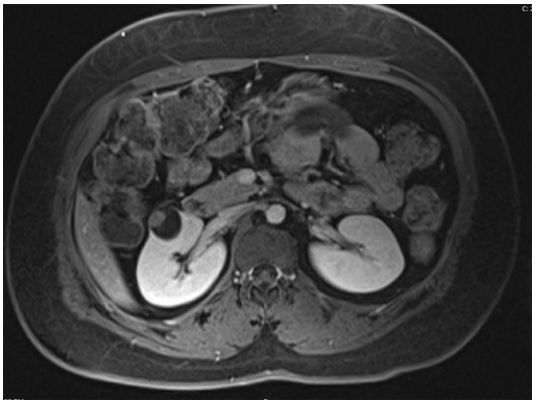

Figure 1. MRI imaging from case 1.

tive, while CD117, CAIX and HMB45 are typically negative [5]. Next-generation sequencing (NGS) analysis of sporadic ESC RCC has revealed somatic mutually exclusive mutations in the *TSC1* and *TSC2* genes [5]. As a rare subtype of renal cell carcinoma with very limited data for molecular evaluation, it is significant to document any new case, especially with a molecular analysis. We describe two ESC RCC cases diagnosed at our institution, one of which had molecular testing performed.

Materials and methods

Case 1

The patient was a 33-year-old female with history of cervical cancer (diagnosed at age 20, excised but no radio-chemotherapy received). A right renal mass was found incidentally on an abdominal ultrasound. The subsequent magnetic resonance imaging (MRI) showed a cystic lesion within the anterior interpolar region of the right kidney measuring up to 2.7 cm and demonstrating an enhancing mural nodule (**Figure 1**). Partial nephrectomy was performed and revealed a fluid filled cyst measuring 2.5 × 2.4 × 1.9 cm which on further sectioning showed a solid yellow tan nodule measuring 1.6 × 1.0 × 0.5 cm, attached to the cyst wall. The nodule has a yellow-tan cut surface. Histology demonstrated solid nests of large tumor cells with abundant eosinophilic to clear cytoplasm (**Figure 2A**). Cytoplasmic coarse granules (stippling) were noticed in the cytoplasm. Rare intranuclear inclusions were also identified. No necrosis or significant mitotic activity were noted. Immunohistochemical stains showed neoplastic cells focally positive for PAX-8, CK20, vimentin (**Figure 2B**), CD10 (**Figure 2C**), Cathepsin K (**Figure 2D**), Racemase, and HMB45 (rare neoplastic cells). Neoplastic cells were negative for CK7, EMA, c-kit, SMA, Melan-A, and TFE3. No molecular testing was available at the time of diagnosis.

Case 2

The patient was a 64-year-old woman with a history of aneurysm of thoracic aorta, dilated cardiomyopathy, and chronic heart failure. She was found to have a left renal mass which increased in size from 2 cm to 4 cm in 2 years by computed tomographic (CT) imaging (**Figure 3A**). She had no flank pain or hematuria. The biopsy of the renal mass favored a diagnosis of ESC RCC. A subsequent partial nephrectomy was done and it revealed a 3.0 × 2.5 × 1.8 cm well-circumscribed soft lesion at the upper pole of left kidney. Serial sections demonstrated a dark red to tan, predominantly solid mass, with focal cystic areas and hemorrhage (**Figure 3B**). Microscopically, the tumor showed distinct solid and cystic architecture (**Figure 3C**); the neoplastic cells had voluminous eosinophilic cytoplasm with cytoplasmic coarse granules (stippling) and were admixed with foamy histiocytes and lymphocytes (**Figure 3D**). There was no true papillary formation, tumor necrosis, prominent vascular network, or substantial mitotic activity. Immuohistochemical studies demonstrated positivity with PAX8 (nuclear, strong and diffusely), CK20 (cytoplasmic, strong and diffusely) (**Figure 4A**), Vimentin (focal) (**Figure 4B**), CD10 (focally) (**Figure 4C**), Racemase (focally, weak), Cathepsin-K (focally) (**Figure 4D**), and CK7 (cytoplasmic, focally weak) and negativity with CAIX, S100, Melan A, HMB45, and CD117. Next generation sequencing (NGS) performed on the resection specimen identified TSC2 p.Gly1172fs (G1172fs) and TSC2 p.Ala1171Pro (A1171P) mutations. Matched normal renal parenchyma was also sequenced, confirming the sporadic setting of this case. No other driver RCC-associated mutations were identified and there were no alterations in gene copy number.

Discussion

In 2016, Trypkov et al. documented a collection of 16 ESC RCC cases with no association with

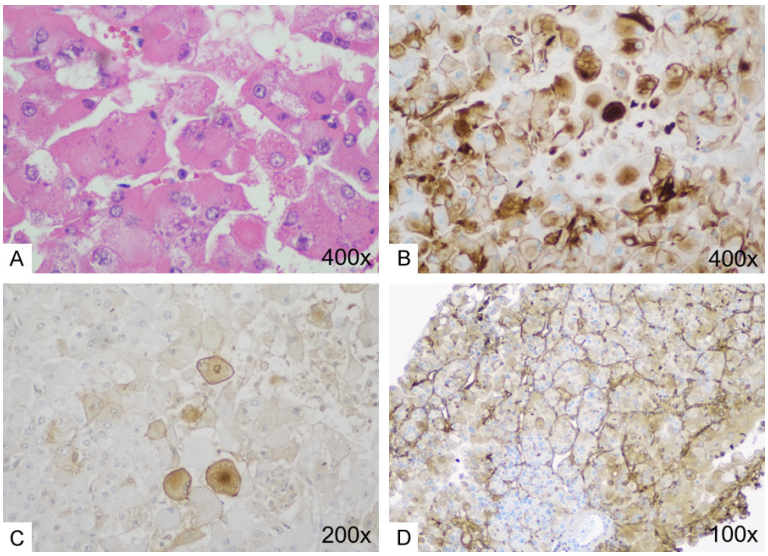

Figure 2. Microscopic features of the tumor (A. H&E, 400×); Immunohistochemical stains show the tumor cells are focally positive for Vimentin (B. 400×), CD10 (C. 200×), and Cathepsin K (D. 100×).

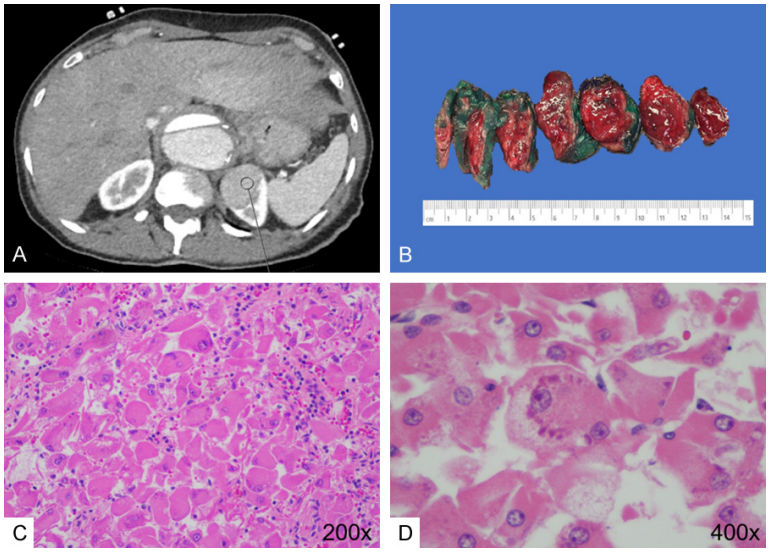

Figure 3. CT imaging from case 2 (A); Macroscopic picture of tumor (B), ruler unit: cm; Microscopic features of the tumor (C. H&E, 200×; D. H&E, 400×).

tuberous sclerosis complex (TSC) - all were sporadic ESC RCC. Trypkov et al. proposed that sporadic ESC RCC represents a novel subtype of renal cell carcinoma, which is found predominantly in female patients and has its own histologic features, distinct immunophenotype (CK20-positive/CK7-negative), and unique indolent behavior. ESC RCC is rare. Although the accurate incidence of ESC RCC is not available yet, the estimated incidence is around 0.2% (4 in 2000) based on their data [4]. In an expanded study by Trypkov et al. in 2017, most institutions identified only 1 to 2 cases after focused searching, even though some of them had a large renal pathology case volume. More cases may be recognized in the future, allowing for better characterization [7]. A recent study of two cases was described by Mohaghegh Poor et al. in 2021 [12]. The clinicopathologic findings of these two reports (17 cases from Trypkov et al. and 2 cases from Mohaghegh Poor et al.) are listed in **Table 1**.

Both of our two cases were female patients, 33 and 64 years old, respectively. Consistent with the findings by Trypkov et al. and Mohaghegh Poor et al., all the patients in these two studies were female. Of note, rare ESC RCC in male patients has been reported in other published literature [10, 11]. Our two cases are within the age range reported by Trypkov et al. and Mohaghegh Poor et al. The ESC RCC lesions were both discovered incidentally in our study, similarly to those reported by Mohaghegh Poor et al., as well as in the majority of documented cases in other studies (no clinical presentation is described by Trypkov et al.). No evidence or history of tuberous sclerosis was found in either of our two cases. One of our patients had a history of cervical cancer. In one published case series, 3 out of 10 patients with sporadic ESC RCC had significant past medical histories (including brain tumor, bladder carcinoma, and sickle cell trait) [11]. Radiographically, one case in our study demonstrated a homogeneously enhancing soft tissue mass while the other case showed a cystic lesion with an enhancing mural nodule (which

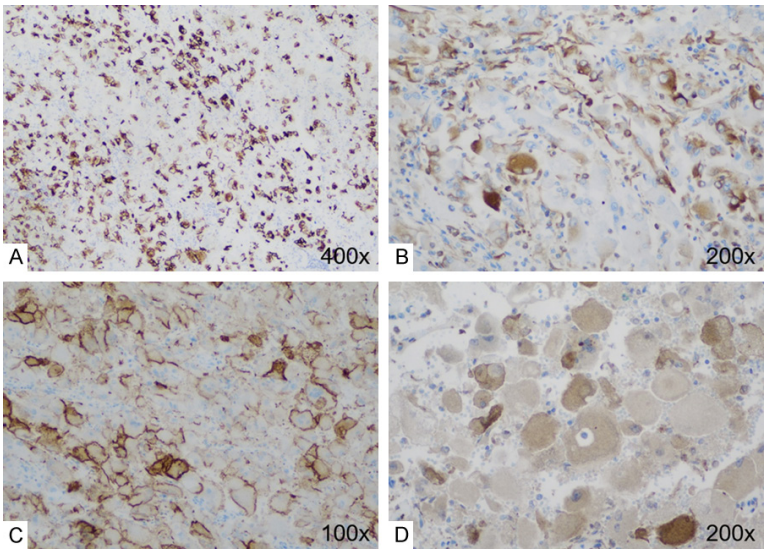

Figure 4. Immunohistochemical stains show the tumor cells are positive for CK20 (strong and diffusely positive, A. 40×), Vimentin (focally positive, B. 200×), CD10 (focally positive, C. 100×), and Cathepsin K (focally positive, D. 200×).

represented the solid component in the resected tumor). No radiographic features were mentioned by Trypkov et al. or Mohaghegh Poor et al. Currently, to the best of our knowledge, there is very limited information regarding radiographic details of ESC RCC. The case 1 patient died of cervical cancer 51 months after resection of the mass of ESC RCC. There was no evidence of recurrence or progression of ESC RCC prior to death. Clinical follow-up of the patient in case 2 showed no recurrence or disease progression at this writing (11 months after resection of tumor).

As a new entity, ESC RCC characterization would benefit from more long-term follow-up data. Rare metastatic cases were reported [8-10], hence the importance of surveillance. ESC RCC is considered to have a good prognosis based on currently available information. Gross examination in our two cases was consistent with the cases described by Trypkov et al. and Mohaghegh Poor et al.: tan with solid and cystic areas. The histopathologic features were also typical: neoplastic cells with voluminous eosinophilic cytoplasm and cytoplasmic stippling. The IHC pattern was also compatible with other studies: CD10 was focally positive in our study, in keeping with the majority of the cases described by Trypkov et al. and Mohaghegh Poor et al. (CD10 positive in 79% and 100%, respectively). Notably, Cathepsin K was reported positive in 62.5% of ESC RCC in a study of young patients with a median age of 27 years (range, 14 to 35 years) [10]. Both our cases showed focal positive Cathepsin K stain in neoplastic cells, with stronger reactivity in case 1. Cathepsin K immunoreactivity in ESC RCC is associated with TSC mutations. The loss or inhibition of the TSC complex causes activation of mTORC1 as well as dysregulation of a number of cell signaling pathways which includes cell growth and proliferation. Inhibition of mTORC1 signaling is known to decrease expression of Cathepsin K in osteoclasts. Therefore, Palsgrove et al. hypothesized that in ESC RCC amplified mTORC1 signaling caused by TSC mutations could augment expression of cathepsin K. Moreover, overexpression of Cathepsin K is common in perivascular epithelioid cell tumors (PEComas) which are also associated with deregulation of the MTOR pathway secondary to mutations affecting *TSC1* or *TSC2* [10, 13]. It has been suggested that Cathepsin K may be used, together with CD10, CK20, and Vimentin, to help with the IHC confirmation of an ESC RCC diagnosis suspected by pathologic examination.

One of our cases was sent for NGS analysis and two variants in *TSC2* gene were identified (TSC2-p.Gly1172fs (G1172fs) and TSC2 p.Ala1171Pro (A1171P) mutations). Although no NGS was performed by Trypkov et al. and Mohaghegh Poor et al., two other studies sequenced sporadic ESC RCC in both pediatric and adult patients by NGS and revealed a consistent presence of TSC1 or TSC2 mutations, that were mutually exclusive [6, 10]. Thus, it has been proposed that TSC1/2 should be a molecular marker of ESC RCC and be used to expand the morphologic spectrum of ESC RCC [10]. It should be noted that a metastatic sporadic ESC RCC case with complete response to everolimus (mTOR inhibitor) in a teenage girl was reported [10]. Recognition of TSC1 or TSC2

Table 1. Comparison between our cases and those discussed in two main studies in the literature

Findings	Case 1	Case 2	Trpkov et al.	Mohaghegh Poor et al.
Sex	Female	Female	All patients are female	Both patients are female
Age (years)	33	64	Median 55 (32 to 79)	Median 41 (38 to 44)
Symptom(s)	Asymptomatic	Asymptomatic	-	Asymptomatic
Radiographic findings	Cystic lesion demonstrating an enhancing mural nodule	Homogeneously enhancing soft tissue mass	-	-
Gross presentation	Fluid-filled cyst with a solid yellow tan nodule attached to the cyst wall	Dark red to tan, predominantly solid with focal cystic areas with hemorrhage	Solid and cystic, yellow-gray gross appearance	Tan-brown, partly solid and cystic
Tumor size	25 mm	30 mm	Median size of 31 mm (range: 12 to 135 mm)	33 to 35 mm
Microscopic presentation	Solid nests of large tumor cells with abundant eosinophilic to clear cytoplasm and cytoplasmic coarse granules (stippling). Rare intranuclear inclusion was also identified	Solid and cystic areas; Voluminous eosinophilic cytoplasm with cytoplasmic coarse granules (stippling) admixed with foamy histiocytes and lymphocytes	Cells exhibiting eosinophilic, voluminous cytoplasm with granular stippling; typically low stage and often show prominent nucleoli	Eosinophilic, voluminous cytoplasm with granular stippling; Prominent nucleoli; Hobnail arrangement of cells lining cysts; Multinucleated cells; Microcystic areas contained eosinophilic proteinaceous material and there were focal aggregates of foamy macrophages
Microscopic necrosis	None	None	-	-
Mitotic activity	None	None	-	-
Metastasis	No	No	None	None
Stage	pT1a	pT1a	Stage pT1 was found in 17/19 (89%) patients	pT1a to pT1b
IHC	PAX8 focally+, CK20 focally+, Vimentin focally+, CD10 focally+, Cathepsin K focally+, racemase focally+, HMB45 rare cells+, CK7-, EMA-, SMA-, Melan A-, CD117-, TFE3-	PAX8 diffusely strong+, CK20 diffusely strong+, Vimentin focally+, CD10 focally+, Cathepsin K focally +, racemase focally weak+, CK7 focally weak+, CAIX-, S100- CD117-, HMB45-, Melan A-	Frequent CK20 positivity, CD10+ or focally+, CK7 negative or only focally positive, CD117-, Vimentin+	PAX8+, CK20 focally+, CD10+, RCC+, Vimentin+, AMACR focally+, CK7-, CD117-
Molecular	Not analyzed	TSC2-G1172fs (p.Gly1172fs) and TSC2 p.Ala1171Pro (A1171P) mutations	Multiple copy gains, copy losses, loss of heterozygosity at TSC1 and copy number gains at TSC2	Not analyzed
Biologic behavior	Died of other cause (cervical cancer)	No local recurrence or metastatic spread to present (9 months) after resection	Indolent behavior; rare cases aggressive (5-10%)	-

mutations in sporadic ESC RCC patients could provide an alternative treatment option to patients who are poor candidates for surgery or whose tumors demonstrate more aggressive behavior [14].

In summary, we analyzed two ESC RCC tumors diagnosed in our institution. Pathologic findings were consistent with those of the small number of published cases. More information about radiologic diagnosis and long-term follow-up will help characterize this tumor.

Disclosure of conflict of interest

None.

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