Case Report

Eosinophilic solid cystic renal cell carcinoma: A series of 3 cases elucidating the spectrum of morphological and clinical features of an emerging new entity

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ABSTRACT

Eosinophilic solid cystic renal cell carcinoma (ESC-RCC) is a recently described entity, which demonstrates distinct clinical, pathological and molecular features. We present a series of three cases, the first to be reported from the Indian subcontinent. All three patients were over 50 years of age; and presented with a large kidney mass. One patient had a locally advanced disease while the other two presented with metastases. Microscopic examination revealed a tumor displaying solid-cystic and/or papillary areas composed of clear as well as eosinophilic cells in all three cases. On immunohistochemistry, all the three cases showed a unique CK20+/α-methyl-acyl-CoA-racemase + immunophenotype. Melan-A was focally positive in Case 2. Cytokeratin 7 was focally but strongly positive in Case 3. The two patients with metastatic disease were diagnosed on core biopsies and were advised oral tyrosine kinase inhibitor therapy. The third patient underwent upfront radical nephrectomy. Due to its peculiar morphology and immunoprofile, the diagnosis of ESC-RCC can be confidently made even on a core biopsy. Most cases reported till date had an indolent course. The metastatic presentation in two of our patients emphasizes the need to gather further evidence to ascertain the biological behavior of this emerging entity.

INTRODUCTION

Eosinophilic solid cystic renal cell carcinoma (ESC-RCC) is an emerging entity, first described by Trpkov *et al.* with characteristic morphology and immunoprofile.[1] It has been proposed that ESC-RCC may be the sporadic counterpart of Tuberous sclerosis-associated RCC.[2] Approximately 60 cases have been reported till date, majority in female patients with a wide age range and an indolent behavior in most of them.[3,4] They have a characteristic morphology and a unique immunoprofile.[1,5] We present three cases of ESC-RCC, the first series to be reported from India.

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CASE REPORT

Case 1

A 55-year-old postmenopausal lady without any co-morbidities presented with severe right-sided flank pain, radiating to the lower limb. Contrast-enhanced computerized tomography (CECT) scan of the abdomen revealed a large irregular lobulated heterogeneously enhancing mass in the right renal fossa measuring 14 cm × 10 cm × 15.5 cm. The mass infiltrated Segment VI of the liver and encased the inferior vena cava (IVC). Computed tomography (CT) angiogram revealed metastatic lesions in the liver and omentum

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[Figure 1a and b]. A CT guided core biopsy, on microscopy, revealed a largely eosinophilic epithelial tumor arranged as small compact nests and acini, separated by a fibrous and myxoid stroma. The tumor cells showed largely monomorphic nuclei with moderately eosinophilic cytoplasm. The nucleoli were distinctly visible at ×400, but inconspicuous at ×100 magnification, International Society of Urologic Pathology Grade 2.[6,7] Focally there were vague cystic structures which were lined by larger clear cells and occasional hobnail cells were also appreciated. On immunohistochemistry, there was a diffuse expression of PAX8, vimentin along with α-methyl-acyl-CoA-racemase (AMACR), however, cytokeratin 7 (CK7) was negative. There was patchy but strong expression of CK20. Melan-A was negative [Figure 2a-h].

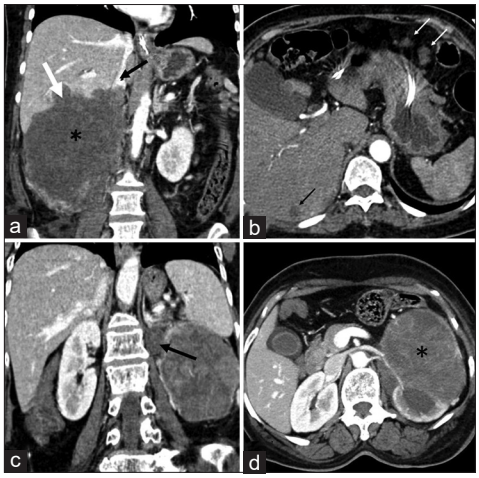

Figure 1: (a) Coronal reconstruction images show a large right renal mass (*) with infiltration of the hepatic Segment VI (white arrows) and inferior vena cava (black arrow). (b) Axial computed tomography images show metastatic lesions in the liver (black arrows) and omentum (white arrows). (c) Coronal reconstruction images show a contiguous left perihilar metastatic node (black arrow). (d) Axial contrast-enhanced computerized tomography study shows a large left renal mass (*) encasing the left renal artery and left renal vein, which are severely narrowed

Based on these distinctive findings, a diagnosis of ESC-RCC was confirmed. The patient was referred for oral tyrosine kinase inhibitor (TKI) therapy in view of the widespread metastasis and unresectable nature of the primary tumor.

Case 2

A 62-year-old female presented with diffuse abdominal pain and painless hematuria for the past 6 months associated with anorexia and weight loss. CECT revealed a heterogeneously enhancing mass in the left kidney measuring 10.6 cm × 10.3 cm × 8.3 cm with tumor extension into the perinephric space with encasement of the hilar vessels and presence of metastatic perihilar nodes [Figure 1c and d]. Positron emission tomography scan showed a hypermetabolic mass in the left kidney (maximum standardized uptake value - SUVma × 12.10) along with necrotic para-aortic lymph nodes and multiple lytic lesions in the cervical and dorsal vertebrae, left proximal femur and bilateral pelvic bones. The histology of the core biopsy revealed linear cores of tumor tissue arranged in predominantly solid (nested) growth pattern with focal but prominent papillary architecture. The tumor cells were large and the nucleoli were distinctly visible at ×100 (ISUP Grade 3). The tumor had an admixture of cells with clear and eosinophilic cytoplasm and diffusely and strongly expressed AMACR and was negative for CK7. The tumor also showed strong, diffuse expression of CK20. There was focal expression of epithelial membrane antigen and Melan-A [Figure 3a-h]. Thus, with the above histology and a characteristic immunoprofile, a diagnosis of ESC-RCC was confirmed. The patient was advised for multi-targeted receptor TKI therapy.

Case 3

A 61-year-old male patient presented with painless hematuria of a month's duration. He was a known diabetic

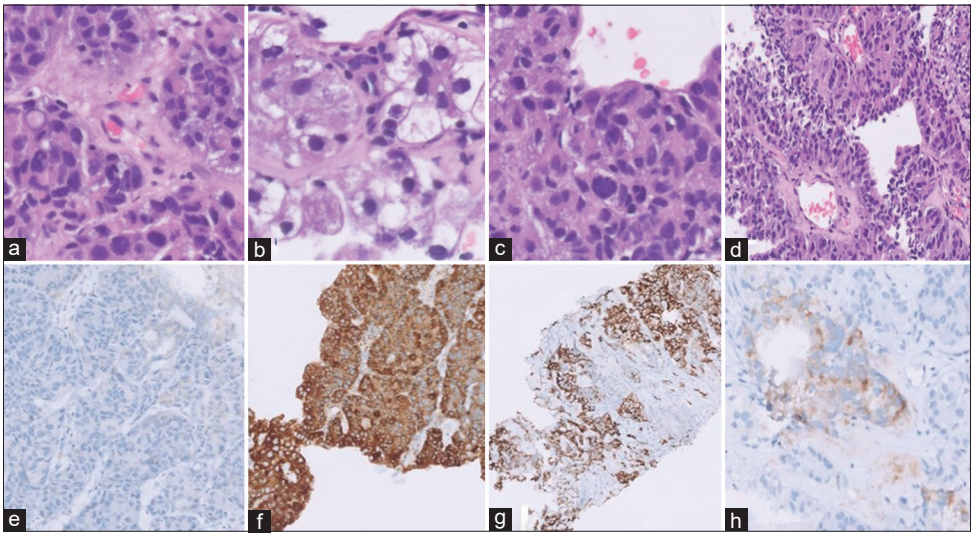

Figure 2: H and E (a-d) Immunohistochemistry (e-h) Photomicrographs of Case 1 (a) The tumor shows presence of eosinophilic cells (×200). (b) Large voluminous clear cells (×200) with (c) moderate nuclear pleomorphism seen (×200). (e) Largely "Type 2 papillary" like areas (×100). On immunohistochemistry, the tumor is (e) cytokeratin 7 negative (×100) while α-methyl-acyl-CoA-racemase (f) and Cytokeratin 20 (g) are diffusely expressed (×100). (h) Melan A shows focal moderate expression (×200)

and hypertensive on medications. CT scan of the abdomen revealed a large heterogeneously enhancing predominantly exophytic mass arising from the left renal upper pole, measuring 8.7 cm × 6.6 cm, invading the renal sinus and extending into the left renal vein for approximately 5 cm. Upfront left radical nephrectomy was performed. Grossly, the tumor was solid and cystic and invaded the renal sinus and renal vein. The sections revealed a classical solid, cystic tumor composed of large cells with abundant granular eosinophilic as well as reticulated/foamy cytoplasm. There were prominent "Type 2 papillary" like areas as well. The cysts were of varying sizes and many had intracystic hemorrhage. Prominent nucleoli were noted at ×100 with foci of binucleation and multinucleation (ISUP Grade 3). There was focal but strong co-expression of CK7 and CK20. AMACR was diffusely positive and Melan A was negative [Figure 4a-h]. The patient is currently under follow up.

DISCUSSION

ESC-RCC is a novel and emerging subtype of RCC, which is currently not a part of the WHO 2016 classification of renal tumors.[6,8] This entity was first mentioned as one of the three morphologies in Tuberous sclerosis associated RCC (TSC-RCC) by Guo *et al*.; viz (1) "renal angiomyoadenomatous tumor" or "RCC with smooth muscle stroma;" (2) RCCs with features similar to chromophobe RCC; and (3) RCCs with a granular eosinophilic-macrocystic morphology.[2] Trpkov *et al*. proposed the existence of "Eosinophilic solid and cystic RCC" as a distinct entity

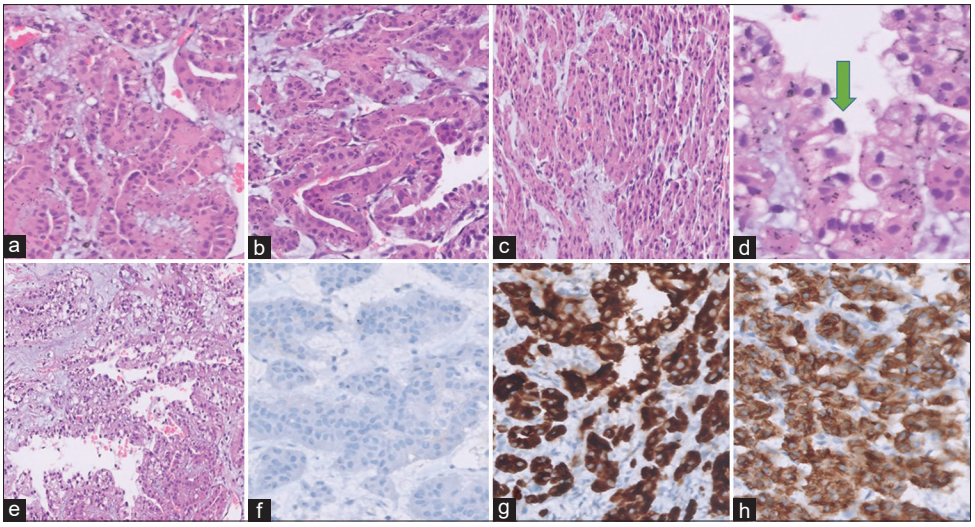

Figure 3: H and E (a-d) Immunohistochemistry (e-h) Photomicrographs of Case 2 (a-c) The tumor shows presence of acinar and solid patterns composed of eosinophilic cells (×200). (d) Clear cells with hobnailing also noted (×200). (e) Tumor largely shows "Type 2 papillary" like areas (×100). On immunohistochemistry, the tumor is negative for distinctly cytokeratin 7 (f) while is diffusely and strongly positive for α-methyl-acyl-CoA-racemase (g) and Cytokeratin 20 (h)

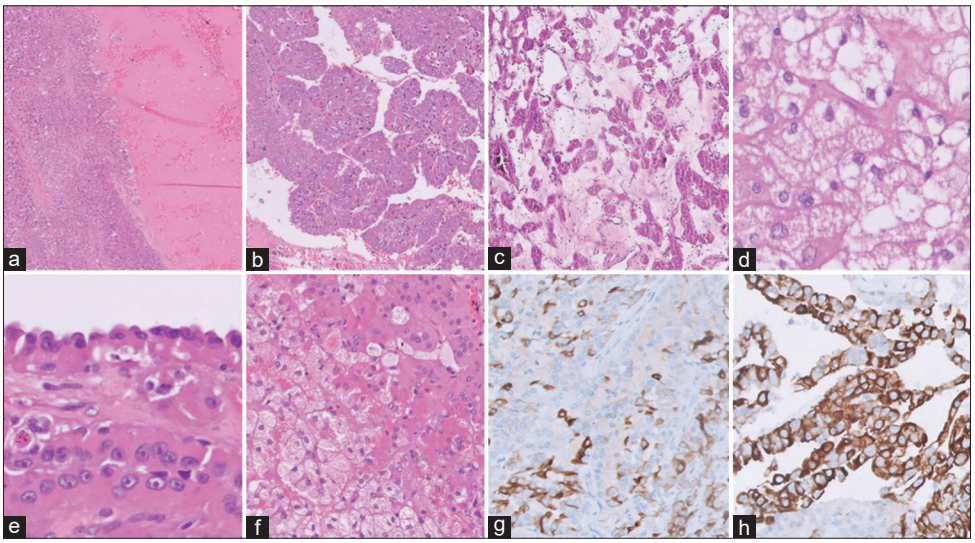

Figure 4: H and E (a-d) Immunohistochemistry (e-h) Photomicrographs of Case 3 (a) Typical solid and cystic areas (×100). (b)"Type 2 papillary"-like areas (×200) and (c) "Oncocytoma-like" areas seen (×100). (e) Large voluminous cells (×400) with (e) Eosinophilic and Hobnail cells present (×400). (f) Histology shows admixture of clear and eosinophilic cells (×200). (g) On immunohistochemistry, cytokeratin 7 is focally expressed (×200) while (h) Cytokeratin 20 is diffusely expressed (×200)

with typical female predilection, indolent behavior, characteristic morphology and immunoprofile (CK7–/CK20+).[1] Subsequent studies have revealed few variant morphologies and the aggressive biological behavior of this subtype.[3,4]

The incidence is currently unknown as many cases have been previously diagnosed as "unclassified RCCs" or other entities.[8] The inceptive studies of ESC-RCC reported a female predilection and an indolent clinical behavior.[1] Later, Li *et al*. and Palsgrove *et al*. reported 10 cases of ESC-RCC in young patients (age range, 14–35 years) and 9 in pediatric patients respectively, with 4 in male patients in the former study.[9,10] Thus, it is now known that ESC-RCC has an extended clinical spectrum and affects adult males, as well as pediatric age group. Till date, very few cases of hematogenous metastasis (lung, liver and bone) have been reported.[4,9,11] The two patients in the current report were females with metastatic disease at presentation. Our first patient (Case 1) had a large locally invasive tumor infiltrating the liver and the IVC along with metastasis to the liver. The second patient (Case 2) also had a large tumor with lymph node (para-aortic) and bone metastasis. Thus, these cases add to the expanding data on the aggressive behavior and metastatic potential of these tumors. The third case (Case 3) presented with locally advanced tumor.

ESC-RCC was classically described to display solid nests and confluent sheets of tumor cells with variably sized macro and microcysts with focal compact acinar or nested growth. The cytological features included voluminous eosinophilic tumor cells that showed prominent granular cytoplasmic stippling, Leishmania Donovani bodies like granular inclusions, large nucleoli, intracytoplasmic vacuolization, multinucleation and hobnail cells in the cystic areas.[5,9] Focal papillary arrangement and clear cell change have also been described.[1,4]

In the current series, the histology in Case 1 demonstrated a solid pattern which consisted of confluent aggregates of tumor cells separated by a fibrous stroma. The aggregates were composed of compact acini and nests in a thin myxoid stroma. The tumor cells were largely eosinophilic, relatively monotonous and showed less cytoplasm than the more common "voluminous" cells. In the cystic areas, clear cells and hobnailing was present. Case 2 demonstrated solid nests as well as papillae with large voluminous cells with prominent cell borders and nucleoli (ISUP Grade 3). The tumor had an admixture of eosinophilic cells and clear cells. The histology of Case 3 was prototypical and it also had oncocytoma-like areas. Areas of "Type 2 papillary" like morphology were seen in Cases 2 and 3, as previously described.[1,10]

ESC-RCC has a characteristic, unique and consistent immunoprofile (CK7–/AMACR+/CK20+).[1,5] The expression of CK20 is a consistent feature of this tumor whereas CK7 is usually either negative or only focally positive.[1,5,8] About 10%–15% of cases can be CK20 negative, but a greater degree of CK7 expression is unusual.[8] Our cases showed the distinctive immunoprofile of CK7–/CK20+ which ruled out the possibility of any other subtype of RCC. CK20 was diffusely and brightly expressed throughout the tumour on both the biopsies. The expression of melanocytic markers (HMB45, Melan-A, Cathepsin-K) is a very intriguing and distinctive finding in ESC-RCC. Cathepsin-K and Melan-A expression seem to be more frequent than HMB45.[4,5] This makes ESC RCCs an important differential diagnosis of epithelioid angiomyolipoma (E-AML) and PAX8 becomes a significant marker to differentiate between these two. Melan-A was positive in one of our cases (Case 2). HMB45 and Cathepsin K were not performed in our series. It must be emphasized that the morphological and immunohistochemical features of ESC RCCs are largely sufficient to distinguish them from not only E-AML but also from other eosinophilic renal neoplasms, namely, MiT family translocation (MiTF RCC-TFEB) RCC, Succinate dehydrogenase deficient RCC, oncocytoma and eosinophilic chromophobe RCC.[3,5]

CONCLUSION

We report the first cases of ESC-RCC, a unique and emerging subtype of RCC, from India. Our cases reiterate that these tumors can behave aggressively. Awareness of this recent entity along with the characteristic morphology and immunoprofile would clinch the diagnosis even on core biopsy samples.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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