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ALK-Rearranged Renal Cell Carcinoma: A Case Report with Review of Literature

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Abstract

Anaplastic lymphoma kinase (*ALK*) rearranged renal cell carcinoma (RCC) is a newly recognized entity in the 2022 WHO classification under molecularly defined renal tumors. It is imperative to diagnose this entity, especially with the advent of *ALK*-directed therapy. Herein, we report the case of a 52-year-old lady who presented with incidentally detected mass in the mid-pole of the left kidney. The patient underwent left radical nephrectomy. Microscopically, the tumor showed varied patterns, namely, papillary, tubulocystic, solid, and varied cell morphologies—cuboidal cells with low-grade nuclei, and rhabdoid cells in nests and clusters. Locoregional spread to the lymph nodes was noted. The tumor was reported as "renal cell carcinoma, unclassified." On further immunohistochemistry, the tumor was diffusely positive for *ALK* by immunohistochemistry. Further, the finding of *ALK* rearrangement was confirmed by fluorescence in situ hybridization, thus confirming the diagnosis of *ALK*-rearranged RCC. She came back with progression after a year and was started on *ALK*-directed therapy after confirmation of *ALK* rearrangement. However, she succumbed to the disease 15 months after diagnosis. *ALK*-directed therapy has revolutionized the management of *ALK*-positive lung adenocarcinomas. Although *ALK*-rearranged RCC is a rare subtype of RCC, it is essential to know this case histopathologically for an accurate diagnosis and future development of targeted therapy.

Keywords

- *ALK*-rearranged renal cell carcinoma
- histopathology
- fluorescence in-situ
- hybridization

Introduction

Anaplastic lymphoma kinase (ALK) rearrangement has been recently described in a variety of solid cancers including anaplastic large cell lymphoma, inflammatory myofibroblastic tumors, non-small-cell lung carcinomas, etc.[1] In renal cell carcinoma (RCC), the subtype *ALK*-rearranged RCC (*ALK*-RCC) was first described by Debelenko et al[2] and Mariño-Enríquez et al[3] in 2011. Since then, many individual case reports and series have been published, which led to the inclusion of *ALK*-RCC as a newly recognized

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entity in the 2022 WHO classification under molecularly defined renal tumors.[4]

ALK rearrangements involving various fusion partners, for example, *NPM-ALK*, *TPM3-ALK*, *EML4-ALK*, etc., have been reported to lead to aberrant *ALK* activation, which has been associated with substantial oncogenic activity.[1] The resultant oncoproteins are expressed in cytoplasmic/membranous patterns. These fusion products have been successfully targeted using tyrosine kinase inhibitors, particularly in non-small-cell lung carcinomas, and this has paved the way for their use in other tumors with *ALK* rearrangement.

We report a case of *ALK*-RCC diagnosed at our center. To the best of our knowledge, this case is the first report of *ALK*-RCC from India, with the current literature review.

Materials and Methods

The patient's clinical details, treatment history, and follow-up data were obtained from the institutional electronic medical record system of Tata Memorial Centre. The biopsy was performed under computed tomography (CT) guidance and the patient underwent radical nephrectomy after the biopsy results confirmed RCC. Immunohistochemistry (IHC) was performed on the Ventana Benchmark XT autoimmunostainer (Ventana Medical Systems Inc., Tucson, AZ, United States). Fluorescence in situ hybridization (FISH) was performed using ZytoVision SPEC ALK dual color, break apart probe (ZytoVision, Bremerhaven, Germany). Interpretation was done on the Olympus BX53F fluorescence microscope (Olympus, Tokyo, Japan), and greater than 15% of the cells showing split green and orange signals was considered positive for ALK gene rearrangement.

Case Report

A 52-year-old woman presented to our tertiary care center with an incidentally detected mass in the mid-pole of the left kidney. The patient's history revealed that the patient had taken consultation elsewhere and was started on sunitinib, which she took for a week before referral to our tertiary care cancer center.

CT scan showed a well-defined solid cystic lesion measuring 4.5 cm in length in the interpolar region of the left kidney with perinephric fat invasion. In addition, enlarged left hilar, left para-aortic, and left aortocaval lymph nodes were also identified. A CT-guided biopsy of the kidney mass was performed. The biopsy was reviewed and after confirmation of RCC, the patient underwent laparoscopic left radical nephrectomy.

Grossly, the specimen revealed a $4.5 \times 4.3 \times 3.5$ cm, grayish-white, ill-defined tumor in the interpolar region of the kidney cortex with extension into the pelvis. In addition, a hilar metastatic lymph node was identified measuring $5 \times 2.5 \times 2.0$ cm, 1 cm away from the primary tumor (►**Fig. 1a**). Histopathology revealed an infiltrating tumor comprising varied patterns, namely, papillary, tubulocystic, and solid. The papillary areas showed fibrovascular cores with foamy macrophages, lined by cuboidal cells with bland nuclei. Few cells showed intracytoplasmic vacuoles. Psammomatous calcification was noted at places. The tubulocystic areas showed tubules filled with mucin—highlighted by the mucicarmine stain. Few areas showed a striking resemblance to thyroid-like follicular RCC with colloid-like material. The tubules were lined by cuboidal cells with low-grade nuclei. These areas were observed to be embedded in a dense

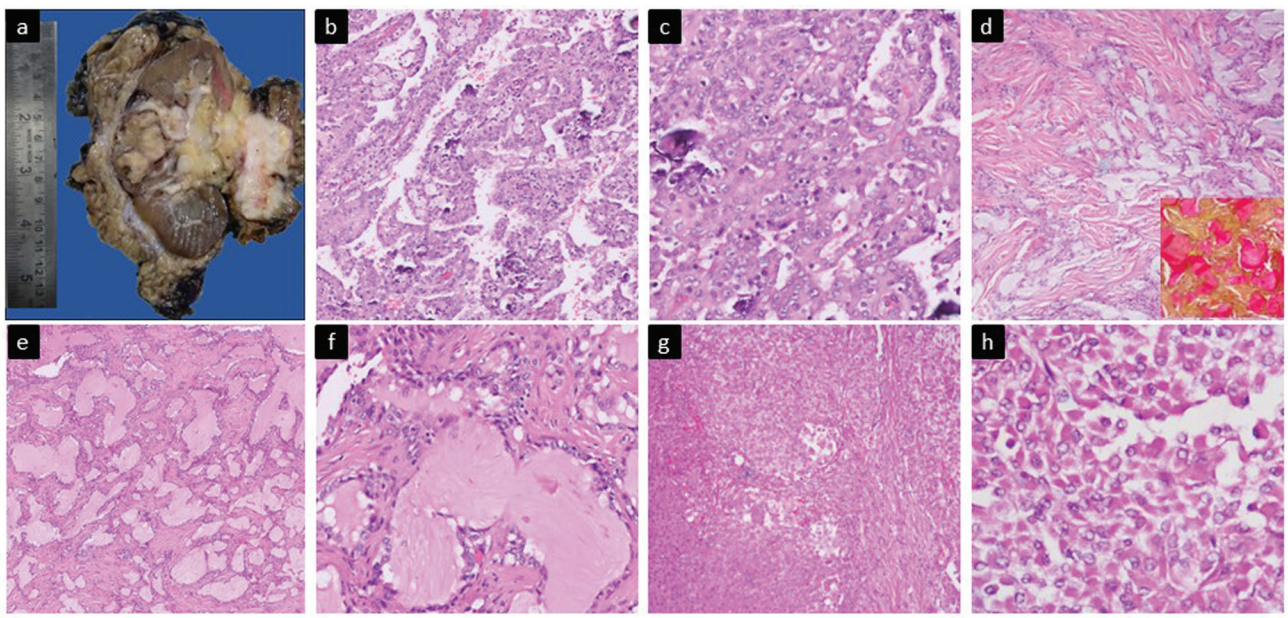

Fig. 1 (**a**) Gross photograph of the nephrectomy specimen. The tumor is seen at the renal hilum with a large metastatic lymph node. (**b, c**) Papillary pattern with foamy macrophages in the fibrovascular cores and psammomatous calcification (hematoxylin and eosin [H&E], 100X); tumor cells with mild nuclear atypia (H&E, 200X). (**d–f**) Mucinous areas with variably sized tubules/glands lined by cells with mild nuclear atypia. The inset shows mucicarmine stain highlighting the mucin within the tubules (H&E, 100X, 200X). (**g, h**) Sheets and nests of tumor cells with rhabdoid features (H&E, 100X, 200X).

desmoplastic stroma. The solid areas comprised an admixture of nests and clusters of rhabdoid cells (►**Fig. 1b–h**). The metastatic lymph nodes showed predominantly the tubulocystic tumor morphology.

On performing IHC, the cells in all the areas were diffusely positive for CK7, AMACR, and PAX8. The cells were negative for HMB45, CK20, TTF1, desmin, ER, p63, and CD10. INI1 was retained. The tumor was reported as "renal cell carcinoma, unclassified" based on the IHC profile.

Further IHC showed the tumor cells were diffusely and strongly positive for *ALK* (D5F3 clone by Ventana; ►**Fig. 2a–e**). Further FISH for *ALK* rearrangement was performed, which showed split green and orange signals consistent with *ALK* gene rearrangement (►**Fig. 2f**).

On follow-up, at 12 months, the patient developed locoregional recurrence and multiple lung and liver nodules with metastatic retroperitoneal supraclavicular lymph nodes. The patient was started on ceritinib 1 year after the diagnosis, but died of the disease within 3 months.

Discussion

ALK is a part of insulin receptor superfamily and is a membrane tyrosine kinase that is expressed only in the central nervous system. Rearrangements involving the *ALK* gene are reported in a variety of cancers and was first reported in 2011 in RCCs.[2,3] To the best of our knowledge, this is the first case of *ALK*-RCC reported from India.

ALK-RCC is reported in pediatric as well as adult RCCs, more commonly in adults. It has been noted that the pediatric cases show homogeneous morphology with predominant areas resembling medullary RCC, while adult *ALK*-RCCs show a heterogeneous morphology, as seen in our case.[5] Overall, the incidence of *ALK* rearrangement in RCC is less than 1%. Hence, screening is difficult.[1] A few cases, predominantly in the pediatric and adolescent age groups, have been reported to be associated with a sickle cell trait.[2,3,6,7] Since the patient was in her 50s and did not present with any signs of the sickle cell trait, we did not investigate its presence in our patient. The physical characteristics of these tumors are that they can be solid or solid-cystic with a whitish to yellowish cut surface.[5] Similar findings were noted in our case. The histological features reported in the literature are extremely variable, which leads to the tumor being frequently labeled as "RCC, unclassified."

However, a few morphological details are conspicuous. The pediatric *ALK*-RCCs have been reported to have a morphology like renal medullary or collecting duct carcinomas.[2,3,6,8] The adult-type RCCs have been reported to exhibit a heterogeneous architecture, comprising papillary, solid, cribriform, tubular, tubulocystic, spindle, etc. The tumor cells also show considerable variation with signet ring cells, rhabdoid, bland cuboidal, or small cell morphology.

Metanephric adenoma-like areas are reported in a few cases.[5] Some studies have reported the presence of intracytoplasmic mucin or a mucinous/myxoid background,

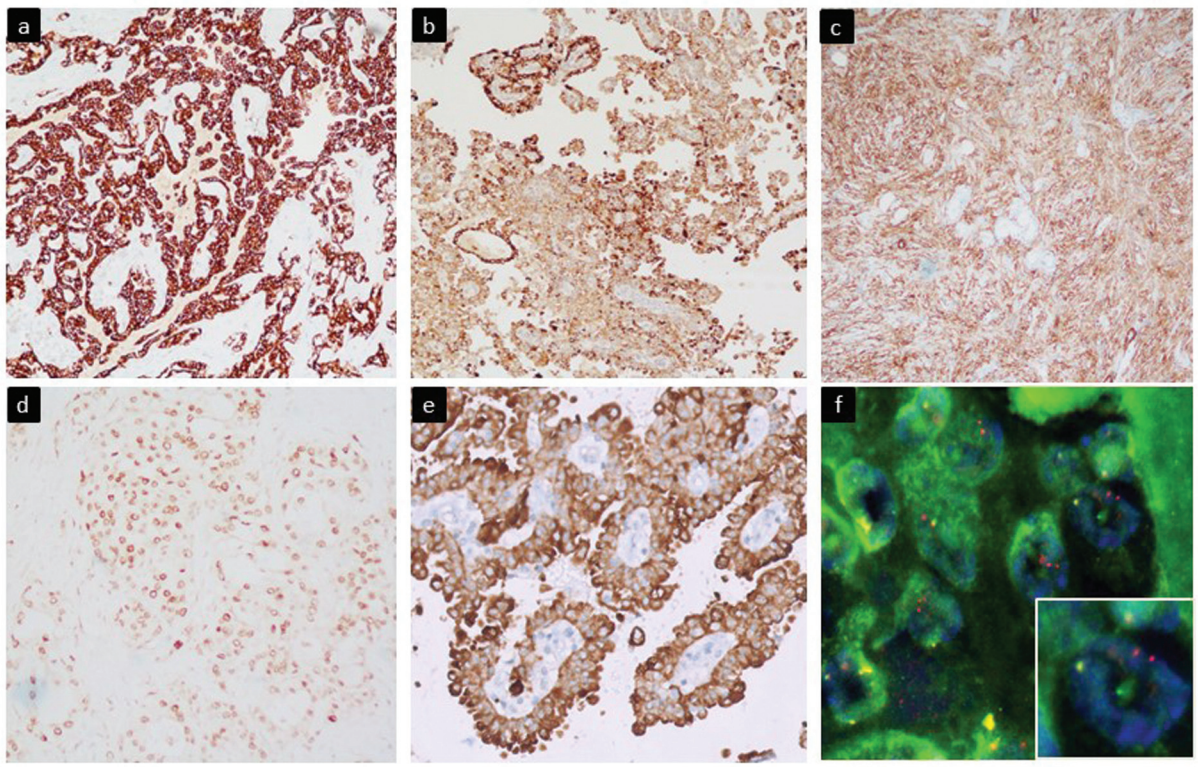

Fig. 2 (**a**) Tumor cells show diffuse positivity for CK7 [3,3'-diaminobenzidine (DAB), 100X]. (**b**) Moderate to strong positivity for AMACR (DAB, 100X). (**c**) The stroma showing diffuse staining for SMA (DAB, 100X). (**d**) Focal nuclear staining for TFE3 in tumor cells (DAB 200X). (**e**) Diffuse strong staining for ALK (D5F3 antibody clone; DAB, 200X). (**f**) Fluorescence in situ hybridization (FISH) rearrangement for ALK with tumor cell nuclei showing split *green and red signals* along with ALK gene copy number gains.

which leads to consideration of mucinous-tubular and spindle-cell RCCs. Our case also showed a heterogeneous morphology with predominantly papillary and tubulocystic areas with focal solid areas.

Cytomorphology was also varied with bland cuboidal cells and rhabdoid cells in the solid areas alongside the presence of mucinous areas. Psammomatous calcification was also noted. Owing to the presence of all these features, we considered performing *ALK* testing.

By IHC, these tumors are CK7, PAX8, and AMACR positive in variable patterns, which are similar to those seen in papillary RCCs. In addition, stains to rule out other subtypes are helpful, like CK20, GATA3, Melan-A, HMB45, and S100. Also, expressions of SDH, FH, and INI1 are retained. Desmin is negative, especially in the rhabdoid areas. *ALK* IHC is a powerful technique for the identification of *ALK* rearrangement, as has already been demonstrated in lung cancers.[4] The *ALK* D5F3 antibody clone showed strong positivity in the tumor cells.

Various molecular methods can be used to confirm the diagnosis of *ALK*-RCCs and these include FISH, polymerase chain reaction (PCR), and next-generation sequencing (NGS). PCR and NGS can convey additional information about the fusion partner; however, break-apart FISH probes cannot be used if identification of the fusion partner is required. It has been shown in various studies that the morphology and immunostaining for ALK are different for different fusion partners.[5,9] We have not performed additional ancillary testing for determination of the fusion partner. Sukov et al have additionally studied the effect of *ALK* copy number gains on the patient outcome—cases with greater than five copies of the ALK gene had a poor outcome.[1] ALK gene copy number gains were also seen in our case.

With the advent of *ALK*-directed therapy, it has become imperative to diagnose this entity accurately. A few cases have been described in the literature where durable responses to *ALK* inhibitors (entrectinib, alectinib) have been documented. Pal et al described three patients who after multiple lines of therapy had a partial and durable response to alectinib (9, 4, and 4 months).[10] Thorner et al report a pediatric patient who was started on an *ALK* inhibitor; however, the patient was still undergoing treatment at the time of publication.[11] This index patient was started on an *ALK* inhibitor, 1 year after nephrectomy; however, she succumbed to the disease due to extensive metastasis.

Because of the rare nature of this tumor, more studies need to be performed to generate evidence on the efficacy of *ALK* inhibitors in *ALK*-RCCs.

A review of all the cases of *ALK*-RCC reported in the literature is summarized in ►**Table 1**.[1–3,5–28]

Conclusion

ALK-RCC is a newly recognized subtype of RCC with clinical and therapeutic importance. It is essential to correctly diagnose this condition. Herein, we have described a few morphological features that can help in accurate diagnosis (in a

Table 1 Review of literature of various cases of ALK-rearranged renal cell carcinoma (RCC)

Sl. no.	Study	Age/sex	Histopathology	Immunoprofile	Metastatic disease	Treatment	Outcome
1	Debelenko et al[2]	16/M	Solid pattern, round to oval nuclei with granular cytoplasm and intracytoplasmic lumina	AE1/AE3, Cam5.2, CK7, EMA, TFE3 positive; CD10, S100, HMB45, WT1 negative	No	Right nephrectomy	NED, 9 mo
2	Mariño-Enríquez et al[3]	6/M	Solid pattern, polygonal to spindle cells with abundant cytoplasm and intracytoplasmic lumina	CK, EMA positive; INI1 retained	No	Right radical nephroureterectomy, paracaval LN	NED, 21 mo
3	Sukov et al,[1] case 1	61/M	Papillary pattern, clear to eosinophilic cytoplasm	AE1/AE3, CK7, EMA, CAM5.2, CD10 (focal), ALK (weak) positive; Napsin-A, HMB45, Melan-A negative	No	Resection	DOD, 48 mo

Table 1 (*Continued*)

4	Sukov et al,[1] case 2	59/M	Papillary pattern, clear to eosinophilic cytoplasm	AE1/AE3, CK7, EMA, CAM5.2, CD10 (focal), ALK (weak) positive; Napsin-A, HMB45, Melan-A negative	No	Resection	DOD, 17 mo
5	Sugawara et al,[12] case 1	36/F	Papillary, tubular, cribriform, solid patterns with focal rhabdoid morphology	AE1/AE3, EMA, CAM5.2, CK7, vimentin, ALK (diffuse, strong), focal for PAX8, PAX2, AMACR, CD10	No	Left radical nephrectomy	NED, 24 mo
6	Sugawara et al,[12] case 2	53/F	Papillary pattern, intracytoplasmic lumina, focal intraglandular myxoid material	AE1/AE3, EMA, CAM5.2, CK7, vimentin, ALK (diffuse, strong), focal for PAX8, PAX2	No	Left radical nephrectomy	NED, 84 mo
7	Lee et al[13]	44/M	Papillary, tubular, solid pattern with abundant eosinophilic cytoplasm	CK, EMA, CK7, PAX2, vimentin, CD10 (focal) positive; CK20, AMACR, C-kit, TFE3, HMB45 negative	No	Radical nephrectomy	NED, 144 mo
8	Smith et al[6]	6/M	Solid pattern, spindle to polygonal cells with abundant cytoplasm and intracytoplasmic lumina	AE1/AE3, CAM5.2, PAX8, ALK (discrete, focal, noncircumferential) positive; HMB45, cathepsin K, p63, CD31, CD34, desmin negative	No	Right radical nephrectomy	NED, 19 mo
9	Cajaiba et al,[8] case 1	16/M	Solid pattern, epithelioid to spindle cells, abundant eosinophilic cytoplasm, intracytoplasmic lumina	AE1/AE3, EMA, vimentin, TFE3, INI1, CK7 (focal) positive; CD10, HMB45, ALK negative	No	Resection	NA
10	Cajaiba et al,[8] case 2	16/F	Solid pattern, epithelioid to spindle cells, abundant eosinophilic cytoplasm, intracytoplasmic lumina	AE1/AE3, CAM5.2, EMA, TFE3, INI1, CD10 (focal) ALK positive; HMB45, Melan-A negative	Regional lymph nodes	Resection	NA
11	Cajaiba et al,[8] case 3	14/M	Solid pattern, epithelioid to spindle cells, abundant eosinophilic cytoplasm, intracytoplasmic lumina	AE1/AE3, EMA, TFE3, INI1, vimentin, CD10 (focal), ALK positive; HMB45 negative	Regional lymph nodes	Resection	NA

(*Continued*)

Table 1 (*Continued*)

12	Cajaiba et al,[14]	16/M	Solid and papillary pattern, epithelioid cells, abundant eosinophilic cytoplasm, intracytoplasmic lumina	EMA, vimentin, CK7, TFE3, INI1 positive	NA	Right radical nephrectomy	NA
13	Jeanneau et al[15]	40/F	Solid pattern, polygonal cells with abundant cytoplasm, vacuolated, rhabdoid cells	AE1/AE3, PAX8, vimentin, INI1, SDHB, ALK, CK7 (focal) positive; HMB45, Melan-A, GATA3, TFE3, AMACR, CD10, CAIX, CD117 negative	No	Left radical nephrectomy	NED, 15 mo
14	Kusano et al,[16] case 1	33/F	Papillary, cribriform, solid pattern, abundant eosinophilic cytoplasm, intracytoplasmic lumina, rhabdoid cells	CK7, PAX8, PAX2, CD10, ALK positive; AMACR, Melan-A, cathepsin K, TFE3 negative	Para aortic lymph node metastases, 120 mo	Right transabdominal nephrectomy, observation for para-aortic lymph nodes	NED, 312 mo
15	Kusano et al,[16] case 2	38/M	Solid, papillary, tubular, cribriform patterns, myxoid areas, eosinophilic cytoplasm, intracytoplasmic lumina, rhabdoid cells, perivascular pseudorosettes	CK7, PAX8, PAX2, CD10, AMACR, TTF1, Napsin A, thyroglobulin, ALK positive; Melan-A, TFE3, cathepsin K negative	Liver, para-aortic lymph nodes, at presentation	Right transabdominal cytoreductive nephrectomy, regional lymphadenectomy, sunitinib	NA
16	Thorner et al[11]	12/F	Solid pattern, anaplastic cells with abundant eosinophilic cytoplasm, pleomorphic nuclei	EMA, TFE3, INI1, AE1/AE3 (focal), ALK positive; CD10, CD68, CD99, S100, desmin, HMB45, WT1, calretinin negative	Locoregional recurrence, 12 mo	Right radical nephrectomy and retroperitoneal lymphadenectomy, ALK inhibitor therapy	AWD, 24 mo
17	Oyama et al[17]	19/F	Pseudopapillary pattern, cuboidal cells with eosinophilic cytoplasm, intracytoplasmic lumina, rhabdoid cells, intraglandular secretions	CK7, AMACR, vimentin, INI1, TFE3 (focal), ALK positive; CD10 negative	No (coexistent Hodgkin's lymphoma)	Right nephrectomy	NED, 16 mo
18	Bodokh et al[18]	55/F	Solid pattern, large cells with eosinophilic cytoplasm, high nuclear grade	CK, vimentin, ALK positive; CD10, CK7, E-cadherin, cathepsin K, Melan-A negative	No (coexistent lobular breast carcinoma)	Right radical nephrectomy	NED, 8 mo

Table 1 (*Continued*)

19	Ross et al[19]	65/M	Papillary and clear cell morphology	NA	Lung metastases at presentation, progressive disease	Nephrectomy, pazopanib, MET inhibitor, everolimus, nivolumab, cabozantinib, alectinib	NA
20	Yu et al,[20] case 1	49/M	Solid sheets, large polygonal cells with abundant cytoplasm, intermediate cells and spindle-shaped cells	AE1/AE3, EMA, vimentin, PAX2, PAX8, TFE3, ALK positive; CK7, AMACR, CD10, CD117, CD68, S100, HMB45, Melan-A negative	No	Left radical nephrectomy	NED, 24 mo
21	Yu et al,[20] case 2	52/F	Papillary pattern with cells with eosinophilic cytoplasm	AE1/AE3, EMA, CK7, vimentin, PAX2, PAX8, ALK positive; TFE3, CD10, CD117, S100, SMA, HMB45, Melan-A negative	No	Left radical nephrectomy	NED, 8 mo
22	Tao et al,[7] case 1	22/M	Rhabdoid and pleomorphic, high nuclear grade	ALK positive	Mediastinal LN, 12 mo	Right radical nephrectomy	AWD, 19 mo
23	Tao et al,[7] case 2	52/F	Chromophobe type	NA	NA	Nephrectomy, pazopanib, nivolumab, lenvatinib, everolimus	NA
24	Tao et al,[7] case 3	54/F	Unclassified RCC	NA	NA	Nephrectomy, everolimus, bevacizumab, nivolumab, cabozantinib	NA
25	Pal et al,[10] case 1	66/M	Papillary and clear cell patterns	NA	Lung metastases, 24 mo	Radical nephrectomy, pazopanib, everolimus, nivolumab, cabozantinib, alectinib	AWD, 54 mo
26	Pal et al,[10] case 2	30/F	Type II papillary RCC	NA	Lung, nodal and bone metastases	Cytoreductive nephrectomy, savolitinib, alectinib	AWD, 9 mo
27	Pal et al,[10] case 3	85/F	Papillary	NA	Lung and adrenal metastases	Carboplatin, paclitaxel, alectinib	AWD, 4months
28	Yang et al,[21]	58/M	Solid, tubular patterns, large nuclei with abundant cytoplasm, cytoplasmic lumina, multinucleate cells	AE1/AE3, EMA, CK7, PAX8, MMR, AMACR (focal), CD10 (focal), INI1, ALK positive; SMA, desmin, HMB45, Melan-A, TFE3, CD31, CD34, ERG, S100, CD117 negative	No	Right radical nephrectomy	NED, 16 mo

(*Continued*)

Table 1 (*Continued*)

29	Wang et al[22]	57/F	Tubular, papillary, tubulocystic, eosinophilic to clear cytoplasm, intraluminal mucin	CK7, E-cadherin, PAX8 (focal), CD10 (focal), FH, INI1, ALK positive; TFE3, TFEB negative	NA	Left radical nephrectomy	DOD, 20 mo
30	Zhu et al[23]	15/F	Papillary pattern, rhabdoid and columnar cells, abundant eosinophilic cytoplasm, stromal mucin	AE1/AE3, PAX8, CD10, vimentin, INI1, TFE3 (focal), AMACR (focal), ALK positive; CD68, WT1 negative	Regional LN	Left radical nephrectomy with lymph node dissection	NED, 10 mo
31	Woo et al[24]	14/M	Solid, tubulo-cystic pattern, epithelioid discohesive cells with abundant cytoplasm, cytoplasmic vacuoles, background mucin	CK, PAX8, CD10, vimentin, TFE3, INI1 positive	No	Left radical nephrectomy	NED, 4 mo
32	Kuroda et al,[5] case 1	33/F	Papillary, trabecular, solid, sarcomatoid, tubules and glands, focal rhabdoid and signet ring cells, cytoplasmic vacuoles, background mucin	CK7, PAX8, INI1, GATA3 (focal), ALK positive; CK20, TTF1, TFE3 negative		Radical nephrectomy	NED, 40 mo
33	Kuroda et al,[5] case 2	51/F	Solid, pseudo-tubular and spindle cells (low grade), background mucin	CK7, PAX8, INI1, vimentin, ALK positive; CK20, TTF1, GATA3, TFE3 negative		Radical nephrectomy	NA
34	Kuroda et al,[5] case 3	25/F	Tubular pattern (metanephric adenoma like)	CK7 (focal), PAX8, INI1, WT1, ALK positive; CK20, TTF1, TFE3, vimentin negative		Partial nephrectomy	NED, 153 mo
35	Kuroda et al,[5] case 4	48/F	Tubulocystic, papillary, trabecular, solid pattern, focal metanephric adenoma-like, rhabdoid cells, signet ring cells, background mucin	CK7, PAX8, INI1, TTF1, vimentin, WT1 (focal), ALK positive; CK20, GATA3, TFE3 negative		Partial nephrectomy	NED, 20 mo
36	Kuroda et al,[5] case 5	54/M	Rhabdoid cells, sarcomatoid morphology, background mucin	CK7, PAX8, INI1, vimentin, ALK positive; CK20, GATA3, TTF1, TFE3 negative		Partial nephrectomy	NA

Table 1 (*Continued*)

37	Kuroda et al,[5] case 6	56/M	Cytoplasmic vacuoles, background mucin	CK7, PAX8, INI1, vimentin, ALK positive; CK20, GATA3, TTF1 negative		Radical nephrectomy	AWD, 66 mo
38	Kuroda et al,[5] case 7	42/M	Papillary pattern, rhabdoid cells, signet ring cells, background mucin	CK7, PAX8, INI1, vimentin, TTF1 (focal), ALK positive; CK20, GATA3, TFE3 negative		Radical nephrectomy	NA
39	Kuroda et al,[5] case 8	58/F	Rhabdoid cells, background mucin	CK7, PAX8, INI1, vimentin, ALK positive; CK20, GATA3, TTF1, TFE3 negative		Radical nephrectomy	NED, 2 mo
40	Kuroda et al,[5] case 9	43/M	Tubular, cords, trabecular, solid pattern, epithelioid and rhabdoid cells, cytoplasmic vacuoles, mucinous tubular areas	CK7, PAX8, INI1, ALK positive; CK20, TTF1 negative		Radical nephrectomy	NED, 12 mo
41	Kuroda et al,[5] case 10	40/F	Tubular, papillary, trabecular patterns, tubules with eosinophilic content (thyroid follicle like)	CK7, PAX8, INI1, vimentin, TTF1, ALK positive; CK20, GATA3, TFE3 negative		Partial nephrectomy	NED, 8 mo
42	Kuroda et al,[5] case 11	38/M	Cytoplasmic vacuoles, signet ring cells, background mucin	PAX8, vimentin, TFE3, ALK positive		Partial nephrectomy	NED, 23 mo
43	Kuroda et al,[5] case 12	68/F	Solid, acinar, tubular, papillary, low grade, metanephric adenoma like	CK7, PAX8, AMACR, FH, vimentin, ALK positive; WT1, CAIX, CK20, GATA3, TTF1, TFE3, INI1 negative		Right partial nephrectomy	NED, 14 mo
44	Chen et al,[25] case 1	38/M	Acinar and glandular pattern, clear cuboidal cells	CAIX, CD10 positive; Ckit, p16 negative	No	Right nephrectomy	NED, 88 mo
45	Chen et al,[25] case 2	59/M	Solid pattern, round to polygonal cells with clear cytoplasm	CAIX, CD10 positive; Ckit, p16 negative	Local recurrence	Left nephrectomy	AWD, 88 mo
46	Wangsiricharoen et al,[9] case 1	14/F	Solid pattern, polygonal cells with abundant eosinophilic and vacuolated cytoplasm, rim of metaplastic bone	PAX8, vimentin, AE1/AE3 (focal), EMA (focal), CK7 (focal), INI1, ALK positive; CD10, CAIX, CD117, SMA, desmin, HMB45, MITF negative	No	Right radical nephrectomy	NA

(*Continued*)

Table 1 (*Continued*)

47	Wangsiricharoen et al,[9] case 2	14/M	Solid, tubular, papillary pattern, eosinophilic cytoplasm	AE1/AE3, CK7, PAX8, vimentin, CAIX (focal), CD117 (focal), ALK, INI1 positive; AMACR, WT1, synaptophysin, Oct3/4, SALL4 negative	Lung metastasis at presentation, subsequent multiple recurrences	Left radical nephrectomy, adjuvant chemo-radiation, sunitinib, re-resection	AWD, 48 mo
48	Sangoi et al[26]	31/F	Solid pattern, pleomorphic cells, rhabdoid to vacuolated cytoplasm, osseous metaplasia	PAX8, vimentin, AE1/AE3, AMACR, GATA3, FH, SDHB, p63 (focal), ALK positive; CK7, CK20, cathepsin K, S100, Oct3/4, CAIX, TTF1, SATB2 negative	No	Right partial nephrectomy	NED, 5 mo
49	Kai et al[27]	42/F	Tubular, papillary, focal spindle, extracellular mucin	CK7, PAX8, vimentin, ALK positive; AMACR, CD10 negative	Regional LN	Left nephrectomy	NED, 24 mo
50	Galea et al[28]	76/F	Solid pattern, rhabdoid, pleomorphic cells with intranuclear inclusions	PAX8, KRT7, AMACR, ALK positive; KRT20, CAIX, KIT, HMB45, Melan-A, TFE3, GATA3, p63, TTF1, thyroglobulin, myogenin, mammaglobin, GCDFP15, negative; SMARCB1, FH, SDH retained	No	Left radical nephrectomy	NED, 10 mo
51	Present case	52/F	Papillary, solid, spindle and mucinous tubular areas, rhabdoid cells, cytoplasmic vacuoles	CK7, AMACR, TFE3 (focal), INI1, ALK positive; Desmin, HMB45, ER, TTF1, CK20, SMA negative	Regional LN; locoregional, liver, lung metastases, 12 mo	Sunitinib, left radical nephrectomy, ceritinib started at recurrence	DOD, 15 mo

Abbreviations: AWD, alive with disease; DOD, died of disease; F, female; M, male; NA, not available; NED, no evidence of disease.

resource-constrained setting) and further referral for relevant ancillary testing. Additional case series and studies are essential to determine the role of *ALK*-directed therapy in these tumors.

Authors' Contributions

G.D. S.M. contributed to the concepts, design, definition of intellectual content, literature search, data acquisition, data analysis, manuscript preparation, manuscript editing, manuscript review, are served as guarantors. A.A., A.K., G.P., A.J., V.M. contributed to the concepts manuscript review, serve as guarantors. S.D. contributed to the concepts, manuscript preparation, manuscript editing, manuscript review, serve as a guarantor.

Patient Consent

The authors certify that they have obtained all appropriate patient consent forms from the patient. In the form, the patient has given written consent for images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflict of Interest

None declared.

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