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Original article

Immune checkpoint inhibitor therapy in metastatic renal cell carcinoma: tumour response and immune-related renal vasculitis following cytoreductive nephrectomy

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Summary

Objective. Therapeutic landscape of metastatic renal cell carcinoma (mRCC) has transformed over the last 2 decades, particularly with the advent of immune checkpoint inhibitors (ICI). While ICI offer therapeutic benefits, they can also provoke immune-related adverse events (iRAEs). Vasculitis as a clinical iRAE from ICI is rare in association with RCC treatment.

Methods. This study included patients treated at our institution with ICI for mRCC (2019-2024). We collected clinicopathologic data and type and duration of immunotherapy. Histologic sections of tumors were re-reviewed by two pathologists to determine pathologic response and features of ICI-related renal injuries.

Results. We identified 8 patients (median age 61.5 years) of which six (75%) presented with metastases at multiple sites, while two had recurrent oligometastatic disease post-partial nephrectomy. All patients were treated with ICI for a duration ranging from 6 to 20 months; 7 patients received combination therapy (CT) [iplimumab & nivolumab (n = 3), pembrolizumab & lenvatinib (n = 2), nivolumab & carbozantinib (n = 1), pembrolizumab & axitinib (n = 1)], while one received monotherapy (MT) (pembrolizumab). Patients were poor surgical candidates at diagnosis (25% Stage 3, 75% stage 4). Six (75%) patients had clear cell RCC (CCRCC), 2 patients had RCC with papillary and eosinophilic features. Tumor necrosis was noted in 75% of cases. Partial tumor response occurred in 7 (87.5%) patients, with 3 (37.5%) achieving tumor downstaging. One patient showed stable primary disease despite resolution of metastatic burden and none of the patients achieved complete response. Three patients (37.5%) had histopathological confirmed renal iRAEs. Two (25%) patients displayed vascular lymphocytic infiltrates, consistent with medium vessels vasculitis; they received CT for 6 months. One patient, who received CT for 20 months, showed a non-necrotizing granuloma.

Conclusions. This study highlights the potential of ICIs for tumor downstaging and disease control in mRCC, though further investigation is warranted to optimize management of iRAEs and long-term outcomes. ICI-associated renal vasculitis is likely underrecognized and underreported highlighting the need for thorough pathological evaluation of non-neoplastic renal tissue in patients receiving ICI.

Key words: immune checkpoint inhibitors, immune-related adverse events, downstaging, vasculitis, granuloma

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Introduction

Renal cell carcinoma (RCC) is among the most prevalent cancers globally, accounting for 90-95% of primary malignant renal tumors [1,2]. Its in-

cidence has risen significantly over recent decades, with GLOBOCAN 2022 reporting an annual incidence of 4,34,840 cases (4.4 %) and 1,55,953 deaths [3]. Approximately 20-30% of patients present with locally advanced or metastatic disease at diagnosis [4]. The National Comprehensive Consortium Network (NCCN 2024) guidelines recommend a multidisciplinary approach for RCC management, including surgery, active surveillance or thermal ablation for early non-metastatic or oligometastatic RCC and palliative therapy for advanced or metastatic RCC (mRCC) [5]. Emerging evidence supports the use of neoadjuvant systemic therapy followed by deferred cytoreductive nephrectomy in patients with mRCC who are poor surgical candidates or have unresectable tumors, as this strategy may facilitate tumour downsizing and/or downstaging [6-8]. The therapeutic landscape for mRCC has evolved significantly over the last two decades, with immune checkpoint inhibitors (ICIs) playing a transformative role. Combination therapies (CT) involving ICIs with another ICI or tyrosine kinase inhibitors (TKIs) have become the standard of care, demonstrating significant efficacy in improving prognosis and achieving complete responses in selected patients. ICIs target key immune-regulatory pathways, such as cytotoxic T-lymphocyte associated antigen-4 (CTLA-4), programmed cell death-1 (PD-1), and PD-ligand 1 (PD-L1), harnessing the immune system to target tumours rather than directly acting on cancer cells [9,10].

Despite their therapeutic benefits, ICIs can induce immune-related adverse events (iRAEs), potentially affecting various organs [11-12]. Common immune-related toxicities include colitis, dermatitis, hypophysitis, pneumonitis, hepatitis, and thyroiditis [13]. Renal involvement, though less frequent, is increasingly recognized, with acute kidney injury (AKI) reported in 0.4–5.0% of cases [14,15]. Acute interstitial nephritis is the most frequently observed kidney pathology, followed by acute tubular necrosis, minimal change disease, vasculitis, glomerulonephritis, and IgA nephropathy [16,17]. While vasculitis in other organs is well-documented, renal vasculitis associated with ICI is rare [16-20]. ICI-associated vasculitis generally has a favorable prognosis, responding well to glucocorticoids and immunotherapy (IO) withdrawal. Awareness of this rare iRAE is essential for clinicians and pathologists alike. Given the limited data on patients receiving ICIs followed by cytoreductive nephrectomy, we aimed to evaluate pathological response, incidence and morphological characteristics of renal injuries in mRCC patients treated with ICIs.

Materials and methods

This retrospective study was conducted following Institutional Review Board approval. A computerized search of our institutional pathology archive (2019-2024) identified eight patients with mRCC who underwent nephrectomy after ICI therapy. Comprehensive clinical data, including demographics, baseline characteristics, comorbidities, imaging results, pathological diagnoses, ICI treatment regimens, duration, adverse effects, and follow-up information, were extracted from electronic medical records. Histologic sections of tumours were re-reviewed by two pathologists to assess ICI-related renal injuries, including vasculitis, granulomas, tubulointerstitial nephritis and glomerulonephritis. Pathological tumour size reduction, downstaging, and final diagnoses were determined per American Joint Committee on Cancer (AJCC). Tumour size reduction was defined as a decrease in the largest diameter of the primary tumour, while downstaging referred to a decrease in the clinical or pathological TNM stage, encompassing changes in tumour size (T), lymph node involvement (N), or distant metastases (M). These assessments were performed by comparing pre-ICI imaging findings with the pathological findings. Treatment responses were evaluated using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria, categorizing outcomes as complete response (disappearance of all target lesions), partial response (≥30% reduction in lesion size), progressive disease (≥20% increase in lesion size or new lesions), or stable disease (not meeting the criteria for partial response or progressive disease).

Results

Demographics and clinical data

Eight patients with mRCC treated with ICIs prior to CN were included. Seven (87.5%) patients were males, with age ranging from 40 to 79 years (median: 61.5 years). Hypertension was present in seven patients, two of whom were also diabetic. Baseline renal function tests (RFTs) were normal before ICI initiation. Six (62.5%) patients presented with metastases at initial diagnosis: in 5, the metastases involved ≥2 sites: lung and bone [patients #3 & #6]; lung and retroperitoneal lymph nodes (RPLN) [patients #4 & #8]; and lung, RPLN and mediastinal LN [patient #5]; one patient [#2] had a lung single-site metastasis. Two remaining patients experienced recurrent disease following partial nephrectomy. One patient (patient #1) had a partial nephrectomy in year 2020, and a radical ne-

phrectomy in 2024 and had only metastatic RPLN with no primary residual/recurrent tumour while patient #7 had a partial nephrectomy in year 2016, and a radical nephrectomy in 2022 with metastasis to RPLN, peri-ureteral implants as along with recurrence at primary site). Based on International Metastatic RCC Database Consortium (IMDC) criteria, 2 (25%) patients were stratified as favourable and 6 (75%) as intermediate risk. All patients were poor surgical candidates at diagnosis (25% Stage 3, 75% stage 4) and received systemic therapy to reduce disease burden and improve long-term outcome.

ICI Therapy and iRAEs

The treatment regimen varied widely across the cohort. Seven patients received combination therapy (CT) with either CTLA-4/PD-1 inhibitors (n = 3) or PD-1/TKI (n = 4), while one patient received anti-PD-1 monotherapy (MT) with pembrolizumab. The interval from initiation of ICI to nephrectomy ranged from 6 to 20 months (median: 9.2). All patients experienced clinical iRAEs, including fatigue, constipation, myalgia, joint pains, mouth pain, pneumonia, dermatitis, gout, diverticulitis and adrenal insufficiency. In 3 of 8 patients, the IO had to be withheld for some time due to severe joint pain, pneumonia and adrenal insufficiency, managed with glucocorticoids. No patients exhibited abnormal RFTs or acute kidney injury (AKI), as determined by creatinine levels or glomerular filtration rate.

Pathological findings and outcomes

Four patients underwent radical nephrectomy (patients # 2,4,5 & 8), 2 total nephrectomy (patients # 3 & 6), and 2 completion nephrectomy (post-partial nephrectomy; patients # 1 & 7). Clear cell RCC (CCRCC) was the predominant subtype (n = 6, 75%,), with the remainder (n = 2) showing RCC with papillary and eosinophilic features (RCC-PapEos). Three (37.5%) tumours were grade 4 (with rhabdoid and/or sarcomatoid features); 3 (37.5%) grade 3, and 1 (12.5%) grade 2, while one patient (#1) showed only metastatic RCC to RPLN (with no residual/recurrent primary tumour), hence was not graded. Tumour necrosis was observed in 75% of cases (5-90%). Partial response (PR) was seen in 87.5% (n = 7), while one patient exhibited stable disease despite resolution of metastatic lesions (patient #2). None achieved a complete response. Tumour downstaging occurred in 37.5% (n = 3; patients # 2,3 & 4), all with CCRCC. Table I summarizes the pre- and post-ICI disease characteristics.

Table I. Pre- and post-ICI disease characteristics.

Patient	Age (yrs)	Gender	Metastatic site at diagnosis	IMDC Risk	Specimen type	Pathologic diagnosis	Rhabdoid features	Sarcomatoid features	Primary renal tumour			Necrosis (%)
									Pre-ICI size on imaging (cm)	Post-ICI size on pathology (cm)	% Tumour reduction	
1	40	M	RPLN	Favourable	CN	Metastatic RCC-PapEos in RPLN	N	N	0	0	#[1]	N
2	68	M	Lung	Intermediate	RN	CCRCC	Y	N	8.9	10	#[2]	60
3	66	M	Lung & bone	Intermediate	TN	CCRCC	N	N	6	1	83	90
4	62	M	Lung & RPLN	Intermediate	RN	CCRCC	Y	Y	10	5.7	43	10
5	68	M	Lung, RPLN & mediastinal LN	Intermediate	RN	CCRCC	N	N	11	10.5	4.5	20
6	67	M	Bilateral lungs & bone	Intermediate	TN	CCRCC	Y	Y	6.6	2	70	5
7	79	M	RPLN & peri-ureteral implants	Intermediate	CN	RCC-PapEos	N	N	*	1.4	#[3]	N
8	42	F	Lung & RPLN	Favourable	RN	CCRCC	N	N	12	9	25	50

RPLN = retroperitoneal lymph node; RN = radical nephrectomy; TN = total nephrectomy; CN = completion nephrectopmy; CCRCC = clear cell RCC; RCC-PapEos = RCC with papillary and eosinophilic features

#[1]Patient 1 (case of post partial nephrectomy) presented with locoregional recurrence with RPLN metastasis only which showed size reduction post-ICI. (there was no residual primary tumour).

#[2] Patient 2 showed improvement in lung nodules post-ICI, however the primary tumour size increased by 12%.

#[3] Patient 7 (case of post partial nephrectomy) presented with locoregional recurrence with RPLN metastasis and peri-ureteral implants which showed size reduction post-ICI. (there was no residual primary tumour).

*Imaging mentioned subtle increased nodularity in perinephric region (exact comment on recurrent primary tumour was not made)

Renal iRAEs post-ICI

Histopathological evidence of renal iRAEs was observed in 3 (37.5%) patients. Two (25%) patients exhibited vascular lymphocytic infiltrates, consistent with medium-vessel vasculitis (classified per the 2012 revised Chapel Hill Consensus Conference nomenclature) (Fig. 1A) [21]. These patients had received CT for 6 months with iplimumab & nivolumab or pembrolizumab & lenvatinib. One patient (12.5%), treated with nivolumab & cabozantinib CT for 20 months demonstrated a non-necrotizing granuloma in the non-neoplastic renal parenchyma (Fig. 1B). All eight patients showed focal glomerulosclerosis, hyaline arteriolosclerosis, and mild chronic interstitial inflammation; however, these findings were attributed to age and hypertension rather than ICI-related effects.

Follow-up data

Follow-up data were available for six of eight patients. Four patients (50%) showed no evidence of disease (NED) over follow-up periods ranging from 2 to 20 months. Two patients (25%) experienced in-

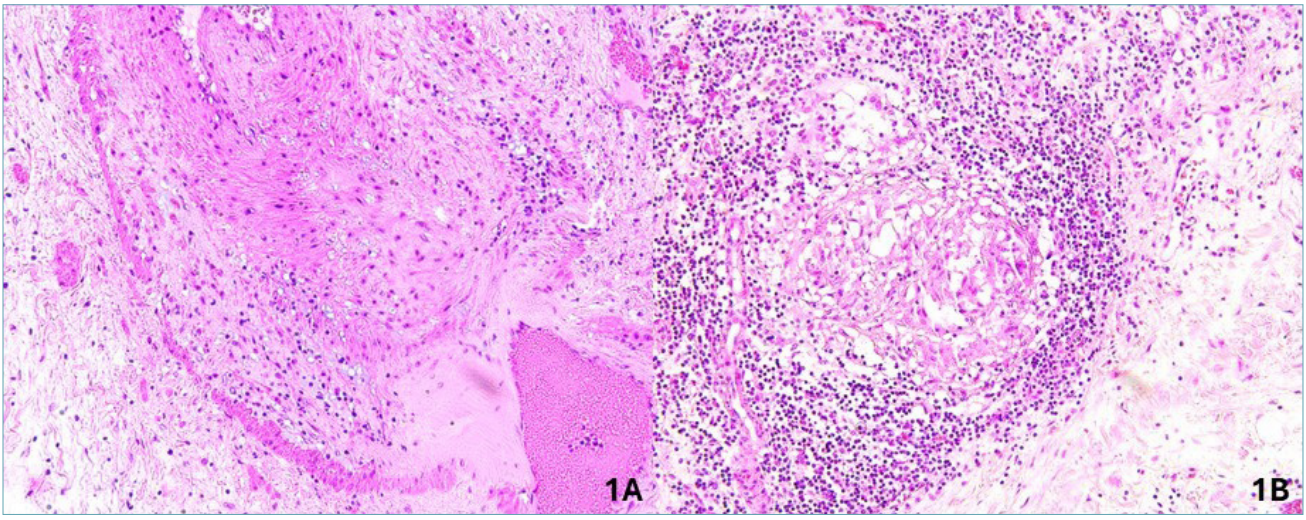

Figure 1. (A) Lymphocytic infiltrate within the vessel wall showing vasculitis in case 2 (H&E x20). (B) H&E from case 3 showing a non-necrotizing granuloma in the renal parenchyma (x20).

Table II. Clinical and renal iRAEs due to ICI along with follow-up.

Patient	c-stage	ICI	ICI duration (months)	iRAEs	p-stage	Vasculitis	Granuloma	Follow-up
1	3	ipilimumab & nivolumab	6	Myalgia, joint pain, significant fatigue, constipation	ypT0N1	Y	N	NA
2	4	pembrolizumab & lenvatinib	6	Fatigue, constipation	ypT3aN0	Y	N	At 2 mths- NED
3	4	nivolumab & cabozantinib	20	Mouth pain	ypT1aNx	N	Y	NA
4	4	ipilimumab & nivolumab	9	Pneumonia, dermatitis	ypT3aN1	N	N	At 6 mths- NED
5	4	pembrolizumab & lenvatinib	8	Gout, diverticulitis, adrenal insufficiency	ypT3aN1	N	N	At 1 yr- PD (Progression of lung nodules, on SBRT)
6	4	Pembrolizumab & axitinib	7	Diarrhoea, cervical arthritis	ypT3aNx	N	N	At 1 yr- PD (new C1 lytic lesions, on SBRT)
7	3	pembrolizumab	9	Fatigue	ypT3aN0	N	N	At 20 mths- NED
8	4	ipilimumab & nivolumab	10	Fatigue, constipation	ypT3aN0	N	N	At 6 mths- NED

NED = no evidence of disease; NA = not available; PD = progressive disease; SBRT = stereotactic body radiation therapy.

terval progression after 12 months: one developed increased pulmonary lesion, while the other presented with a new C1 vertebral lytic lesion (both are undergoing stereotactic body radiation). No fatalities due to vasculitis or cancer progression were reported during the follow-up period. Table II summarizes the identified iRAEs due to ICI and follow-up outcomes.

Discussion

Cytoreductive nephrectomy (CN) remains a pivotal component in the management of mRCC. The advent of systemic therapies, including ICIs, has revolutionized the treatment paradigm, with pre-CN systemic therapy offering significant tumour burden reduction and improved patient outcomes. However, these therapies are associated with iRAEs, including nephrotoxicity, which occurs in up to 5% of patients receiving ICI therapy [14-16]. Among these, ICI-associated vasculitis is a rare complication, and renal vasculitis specifically is even less common [16-20]. The exact mechanisms underlying ICI-associated renal toxicity are not fully elucidated. Potential mechanisms include direct lymphocytic infiltration of the renal interstitium, immune complex-mediated injury, lupus nephritis, IgA nephropathy, microangiopathy, or cytokine release causing podocyte damage and resultant glomerular pathologies such as minimal change disease and focal segmental glomerulosclerosis [17]. For vasculitis, increased T-cell activity against antigens, increased levels of autoantibodies, inflammatory cytokines, and complement-mediated injury have been implicated. Genome-wide association studies suggest a genetic predisposition, while T-cell-mediated promotion of anti-neutrophil cytoplasmic antibodies (ANCA) may play a significant role in the pathogenesis of pauci-immune vasculitis [22-24]. A literature review identified only 18 confirmed cases of ICI-associated renal vasculitis to date (Tab. III) [25-35]. All were diagnosed based on

Table III. Overview of patients showing renal vasculitis post-ICI from previously published cases along with current cases.

Case reference	Cancer type	Age	Sex	IO	iRAEs	Onset after therapy initiation	Type of vasculitis	Chapel-Hill classification	ANCA status	Follow-up/ Tumor status
Casafont-Sole et al., 2020[25] Case 1	Lung (SCC)	64	M	Durvalumab	Erythematous macules, papules; pedal edema	5.75 mths	IgA vasculitis	Small vessel vasculitis	ANCA-	SD (not on treatment)
Aqeel et al., 2022[26] Case 2	Palatine tonsil (SCC)	65	M	Pembrolizumab	Haematuria, proteinuria, foot drop	5 mths	AAV	Small vessel vasculitis	p-ANCA+ (MPO)	PD (Died)
Aqeel et al., 2022[26] Case 3	Lung (SCC)	67	F	Pembrolizumab	haematuria, proteinuria	1 mth	AAV	Small vessel vasculitis	ANCA+ (PR3)	PD (on chemotherapy)
Hung et al., 2021[27] Case 4	Melanoma (recurrent)	66	F	Nivolumab + ipilimumab	Headache, polyarthralgia, palpable purpuric rash, proteinuria, hemoptysis	0.75 mth	AAV	Small vessel vasculitis	c-ANCA+	NA
Laamech et al., 2021[28] Case 5	Lung (Adenocarcinoma)	81	M	Nivolumab	Fatigue, fever, dyspnea	18 mths	AAV	Small vessel vasculitis	p-ANCA+ (MPO)	SD
Belkaid et al., 2020[29] Case 6	Melanoma	70	M	Nivolumab + ipilimumab	Palpable purpura, abdominal pain, diarrhoea, arthralgia	7.75 mths	IgA vasculitis (HSP)	Small vessel vasculitis	ANCA-	SD
Ishimura et al., 2020[30] Case 7	Melanoma	67	F	Nivolumab + ipilimumab	Fever, chills, diarrhoea	2 mths	Granulomatous arteritis	Not classified	ANCA-	NA
Person et al., 2020[31] Case 8	Melanoma (anal mucosa)	55	M	Nivolumab + ipilimumab	Fever, rash, dyspnea, dry cough, oliguria	2 mths	Arteriolar vasculitis with TMA- like thrombi	Not classified	NA	PD

Gallan et al., 2019[32] Case 9	Melanoma (anal mucosa)	68	M	Nivolumab	Fever, dyspnea, myalgias	0.5 mths	Vasculitis (arcuate & interlobular arteries)	Not classified	NA	Died due to vasculitis
Gallan et al., 2019[32] Case 10	Lung (NSCLC)	75	F	Nivolumab	AKI	24 mths	Renal vasculitis (arcuate artery)	Not classified	ANCA-	NA
Gallan et al., 2019[32] Case 11	Melanoma (choroidal)	63	F	Nivolumab	Fever, fatigue, AKI	3 mths	Renal vasculitis (interlobular artery)	Not classified	ANCA-	NA
Lemoine et al., 2019[33] Case 12	Melanoma (anal mucosa)	70	M	Nivolimumab then ipilimumab	Fatigue	13.6 mths	Focal segmental granulomatous arteritis	Not classified	ANCA-	PD (Died)
Mamlouk et al, 2020[34] Case 13	Lung (NSCLC)	40	M	Nivolumab	Hematuria, proteinuria, pyuria	5 mths	Focal crescentic GN, focal global GS	Small vessel vasculitis	ANCA-	PD (Died) – 4 mths
Mamlouk et al, 2020[34] Case 14	mRCC	70	M	Tremelimumab	Cough, hematuria, dermatitis	2 mths	Focal crescentic GN, focal global GS	Small vessel vasculitis	p-ANCA+ (MPO)	PD (on TKI) - 12 mths
Mamlouk et al, 2020[34] Case 15	Melanoma	60	F	Nivolumab + Ipilimumab	Fatigue, poor appetite	3 mths	Diffuse global GS, granuloma	Small vessel vasculitis	ANCA-	Died, 8 mths
Mamlouk et al, 2020[34] Case 16	Liposarcoma	60	M	Nivolumab	Hematuria, proteinuria,	2 mths	Focal crescentic GN, focal global GS	Small vessel vasculitis	ANCA-	SD- 12 mths,
Mamlouk et al, 2020[34] Case 17	Melanoma	50	F	Nivolumab, ipilimumab	Proteinuria	2 mths	Diffuse necrotizing GN with IgA deposits	Small vessel vasculitis	ANCA-	SD- 4 mths
Cortazar FB et al, 2016[35] Case 18	Melanoma	58	M	Iplimumab	None	5 mths	TMA	Small vessel vasculitis	NA	NA
Case 19 (Current study; patient 1)	mRCC	40	M	Nivolumab, ipilimumab	Myalgia, joint pain, significant fatigue, constipation	6 mths	-	Medium vessel vasculitis	NA	NA
Case 20 (Current study; patient 2)	mRCC	68	M	Pembrolizumab, lenvatinib	Fatigue, constipation	6 mths	-	Medium vessel vasculitis	NA	NED- 2 mths

NSCLC: Non-small cell lung carcinoma, RCC: Renal cell carcinoma, AAV: ANCA-associated vasculitis, SD: Stable disease, PD: progressive disease, TMA: Thrombotic microangiopathy, GN: Glomerulonephritis, GS: Glomerulosclerosis, AKI: Acute kidney injury, NA: Not available, NED: No evidence of disease

histopathology confirmed kidney biopsy post-iRAEs manifestation. This study is the first to systematically evaluate renal iRAEs, particularly vasculitis, in nephrectomy specimens following ICI therapy.

In this cohort, renal iRAEs were noted in 37.5% of patients (n = 3), markedly higher than the < 10% reported in other cohorts [10,14,15]. All three cases were associated with CT, suggesting a higher risk of renal complications with combination therapies as documented by prior studies [36]. Renal vasculitis was observed in 25% (n = 2) of cases, higher than the < 5% reported in prior studies [18,19]. Both cases involved medium-vessel vasculitis, contrasting with the predominance of small-vessel vasculitis in previously published renal vasculitis cases [25-35]. This divergence also contrasts with ICI-associated vasculitis in non-renal sites, which predominantly involves large and medium-sized vessels [18]. Interestingly, clinical presentations of renal vasculitis, such as AKI or hematuria, were absent in these patients. Both cases were associated with PD-1 pathway inhibition (PD-1+TKI and PD-1+CTLA-4), aligning with prior studies indicating that PD-1 deficiencies may predispose patients to inflammatory vascular injury [37]. The time to vasculitis onset ranged from six months in this study to two years in prior reports, underscoring the variability in presentation timing. Notably, ANCA serology, often assessed in vasculitis cases, was unavailable in these patients, limiting conclusions about ANCA association. In previous reports, ANCA positivity was detected in 28% (5/18) of cases, with no clear

link to specific ICIs [25-35]. Granulomatous inflammation was identified in one patient (12.5%), consistent with prior reports showing an incidence of 21-23% [35,36]. Granulomas were not associated with acute interstitial nephritis (AIN) in this study, diverging from previous findings where granulomas typically co-occurred with AIN [36,38]. This may reflect a hypersensitivity or delayed immune response triggered by ICI therapy.

ICI therapy demonstrated significant efficacy, with 62.5% of tumours showing pathological downsizing (median tumour size reduction: 45.1%) and 87.5% of patients achieving a partial response (PR). These findings surpass prior studies reporting downstaging rates of 44% and median size reductions of 17.8%-10.2% [40,41]. However, no complete responses (CR) were observed in this cohort, unlike the 10%-15% CR rates previously documented [40]. Patients with aggressive tumour features (e.g., rhabdoid and sarcomatoid features) also responded favorably, with two of three showing PR and no disease progression on follow-up [42,43]. Combination therapy (CT) with nivolumab and ipilimumab was associated with high efficacy, consistent with prior studies indicating favorable outcomes in 40% of patients [44].

Conclusion

This study highlights the potential of ICIs for tumour downsizing/ downstaging and disease control in mRCC along with an increased incidence of renal vasculitis and other iRAEs in patients receiving ICI therapy prior to CN. Medium-vessel vasculitis and granulomatous inflammation represent rare yet significant pathologies that clinicians and pathologists should recognize. ICI-associated renal iRAEs are likely underrecognized and underreported highlighting the need for thorough pathological evaluation in patients receiving ICI. Our findings underscore the need for vigilant monitoring and a multidisciplinary approach to manage these complex cases effectively.

Conflict of interest statement

The authors declare no conflicts of interest.

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Ethics approval

Yes, per institutional IRB (IRB-140724007).

Authors contribution

All authors contributed to the publication according to the ICMJE guidelines for the authorship (study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision). All authors read and approved the submitted version of the manuscript.

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