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Spontaneous regression of metastatic clear cell renal cell carcinoma: A report of a rare case and a review of the literature

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A B S T R A C T

Renal cell carcinoma (RCC) is the seventh most common cancer in the United States; clear cell RCC (ccRCC) is the most common subtype. We report a case of spontaneous regression of metastatic ccRCC and discuss possible underlying mechanisms informed by a literature review. While regression of metastatic RCC has been described following nephrectomy or treatment of the primary tumor, spontaneous regression is rare. Postulated underlying causes include tumor necrosis and immune-mediated responses. Of 29 identified cases of spontaneous regression, only ours occurred after only a biopsy. Better understanding of the pathophysiology of spontaneous regression in RCC will improve its management.

1. Introduction

Cancers of the kidney and renal pelvis are the 7th most common cancer in the United States, with an estimated 81,610 new cases and 14,390 deaths projected in 2024.[1] Clear cell renal cell carcinoma (ccRCC) is the most common kidney cancer in adults, accounting for ~75 % of all renal cell carcinoma (RCC).[1] While the 5-year relative survival is 93.3 % for localized RCC, it is 18.2 % in the metastatic setting.[1] Computed tomography (CT) and magnetic resonance imaging (MRI) can help diagnose RCC, but tissue biopsy remains the gold standard. The intricate relationship between RCC and the immune system has long been acknowledged, prompting numerous endeavors to modulate immune responses. The emergence of tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICPIs) has revolutionized therapy for metastatic ccRCC, significantly improving both overall and progression-free survival. Current treatment guidelines for metastatic RCC (mRCC) recommend ICPI doublets or ICPI and TKI combination therapy.[2]

Spontaneous regression of cancer refers to the complete or partial disappearance of a malignant tumor without anti-neoplastic treatments, and is most commonly reported in RCC, carcinoma of the breast, and melanoma.[3]

2. Case presentation

A 52-year-old male presented with right flank pain, and progressively worsening clinical condition leading to inability to work. His medical history was notable for idiopathic pulmonary fibrosis and type 2 diabetes mellitus. Family history was significant for a paternal history of brain cancer. He had occupational exposure to sand blasting, aluminum, and industrial cleaning products, and no history of tobacco, intravenous drug, or alcohol use. Initial imaging via computed tomography (CT) scan revealed a 12 × 10 cm heterogeneously enhancing left renal mass, along with enlargement of the left renal vein. Additionally, a heterogeneous mass was identified in the right paraspinal muscle, accompanied by prominent retroperitoneal lymphadenopathy and bilateral pulmonary nodules, indicative of metastatic disease. MRI of the thoracic spine detected a 14 x 8.5 × 3.5 cm soft tissue mass in the right paraspinal muscle extending from T9 to L1 vertebrae (images not shown). Histopathological examination of the left renal mass via CT-guided core needle biopsy showed sheets of tumor cells with focal clear cell changes (Fig. 1A). Immunohistochemical stains (Fig. 1B) performed were positive for CA-IX, PAX-8 with patchy AMACR expression and negative for

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List of abbreviations

RCC	renal cell carcinoma
ccRCC	clear cell renal cell carcinoma
mRCC	metastatic renal cell carcinoma
CAP	chest and abdomen/pelvis
CT	computed tomography
ICPI	immune checkpoint inhibitor
MRI	magnetic resonance imaging
TKI	tyrosine kinase inhibitor
TN	tumor necrosis

CK7, p63, and GATA3 consistent with a diagnosis of ccRCC with extensive necrosis. Similarly, biopsy of the paraspinal muscle mass revealed ccRCC with rhabdoid changes (Fig. 1C and D). The MRI findings were confirmed by CT scans of the chest and abdomen/pelvis (CAP) (Fig. 1A and B). Next-generation sequencing of paraspinal muscle mass tissue identified a Von Hippel-Lindau mutation (Exon 2) and Polybromo-1 mutation.

Laboratory results showed a hemoglobin level of 9.6 g/dL (reference range: 13–18 g/dL), calcium level of 8.9 mg/dL (reference range: 8.7–10.1 g/dL), absolute neutrophil count of 10.11 K/mm^3 (reference range: 1.6–8.6 K/mm^3), and platelet count of 529 K/mm^3 (reference range: 140–440 K/mm^3). These findings, coupled with his immobilized state, categorized him into the poor-risk prognostic group according to the International Metastatic Renal Cell Carcinoma Database Consortium Criteria.[2] Following discussion in the multidisciplinary tumor board, the decision was made to pursue palliative radiation for the unresectable paraspinal muscle mass to alleviate flank pain. However, before initiating systemic therapy, he was admitted due to severe anemia (hemoglobin 6.7 g/dL) and chest pain, accompanied by elevated troponin T [35 ng/L (reference value: <15 ng/L)] and nonspecific ST elevations on electrocardiogram. CT CAP revealed worsening pulmonary nodules, mediastinal lymphadenopathy, persistence of the left renal mass, new liver lesions, and cardiac lesions. Echocardiogram findings raised concerns about a right ventricular mass suggestive of metastatic disease and intraventricular thrombosis. Notably, CT CAP showed a significant decrease in the size of the paraspinal muscle mass (Fig. 2). After receiving packed red blood cells and initiating treatment with apixaban for thrombus management and antibiotics for suspected infection, he was discharged. Upon follow-up in the clinic (57 days post-biopsy), he reported significant improvement in flank pain and interim enhancement in performance status, even prior to systemic treatment.

The patient was subsequently started on nivolumab and ipilimumab one-week post-discharge. However, this regimen was complicated by the development of pneumonitis, necessitating steroid therapy and discontinuation of further ipilimumab. Upon repeat CT CAP, a complete response was observed in the paraspinal muscle mass, along with improvements in the renal mass and retroperitoneal lymphadenopathy, while mediastinal lymph nodes, cardiac, and pulmonary metastatic lesions remained stable. The patient underwent three additional cycles of single agent nivolumab before discontinuing treatment due to recurrent pneumonitis. The patient transitioned to the TKI cabozantinib, which he tolerated well with no evidence of disease progression over the ensuing 12 months.

2.1. Literature review

Alongside our case, our literature search (Fig. 3) identified 29 previously reported cases of spontaneous regression of ccRCC (Tables 1 and 2). All cases were confirmed as ccRCC through biopsy of at least one metastasis and none received systematic treatment prior to regression. Of metastatic sites, the lung was the most common site of spontaneous regression (66.7 %, n = 20), followed by lymph nodes (26.7 %, n = 8), bone (6.7 %, n = 2), liver (6.7 %, n = 2), renal (6.7 %, n = 2), and muscle

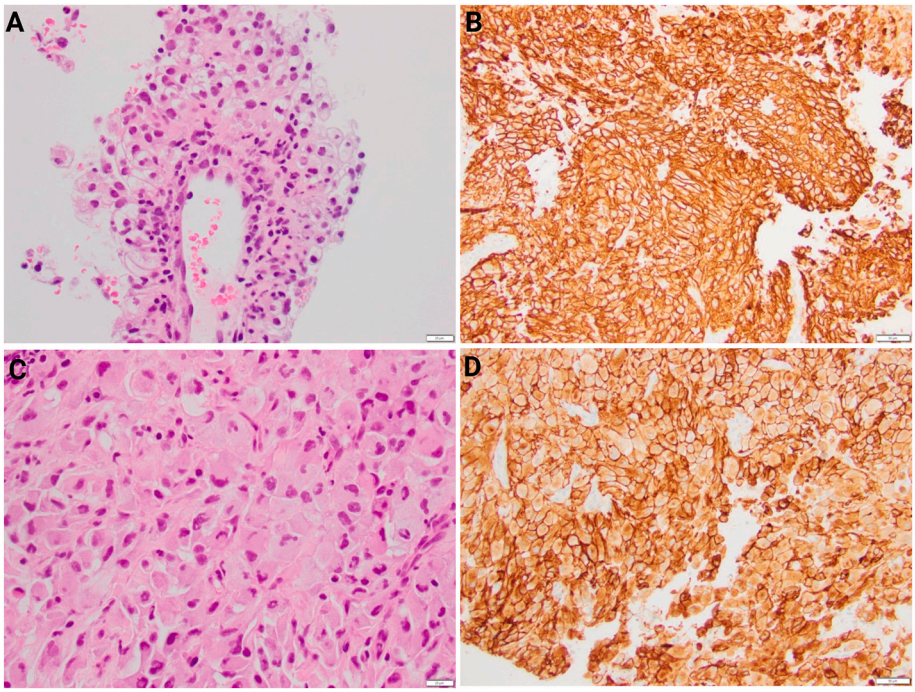

Fig. 1. Histopathology images. (A) H&E, 400× magnification of renal mass, tumor cells are polygonal with eosinophilic cytoplasm with focal clear cell changes. Nuclei appear pleomorphic with ovoid to irregular nuclear contours, moderately condensed chromatin and variably prominent nucleoli. (B) CA-IX immunohistochemical stain, 200× magnification of renal mass, Diffuse positive in tumor cells (complete membranous staining). (C) H&E, 400× magnification of paraspinal muscle mass, tumor cells have low nuclear cytoplasmic ratio with eosinophilic cytoplasm and eccentrically placed nuclei (rhabdoid features). Nuclei appear pleomorphic. (D) CA-IX immunohistochemical stain, 200× magnification of paraspinal muscle mass, Tumor cells are diffusely positive.

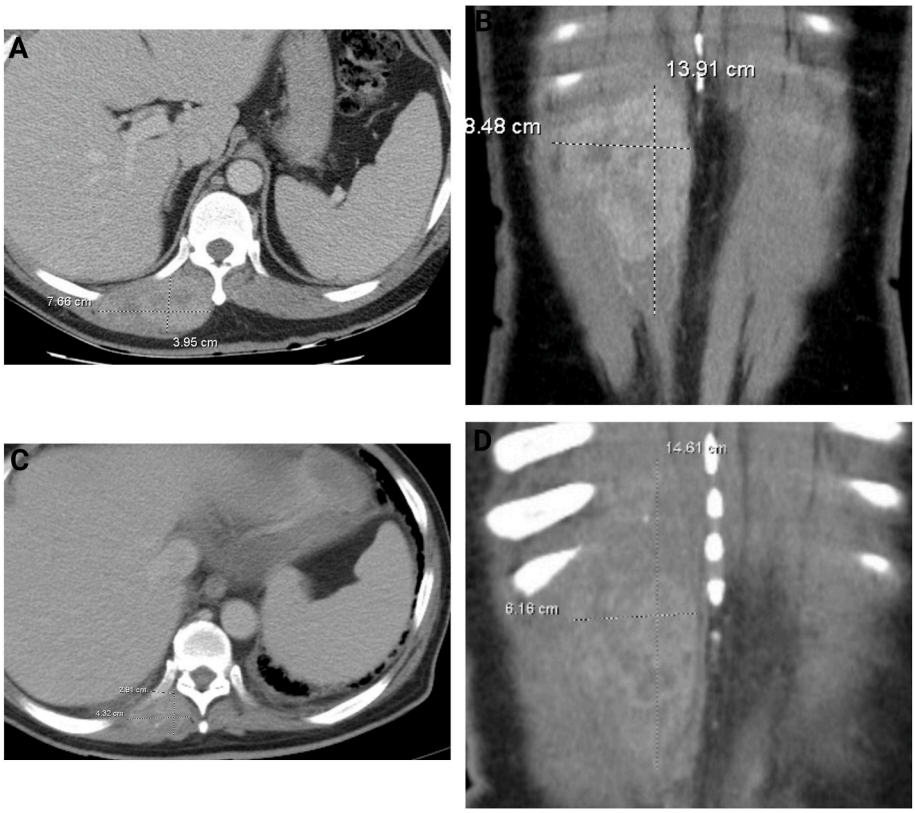

Fig. 2. Computed tomography with contrast of the paraspinal muscle mass. Axial view (A) and coronal view (B), original scan from outside study performed on 5/12/2022. Axial view (C) and coronal view (D), follow up scan on 8/15/2022.

(6.7 %, n = 2). Nearly all patients (93 %, n = 28) had undergone nephrectomy before experiencing spontaneous regression. Notably, one patient exhibited spontaneous regression of the primary tumor before nephrectomy, mirroring our reported case. 63.3 % (n = 19) showed complete regression of the metastatic burden, while 36.67 % (n = 11) demonstrated partial regression of metastases.

3. Discussion

The spontaneous regression of metastatic lesions in cancer presents a compelling anomaly, challenging conventional notions of disease evolution and therapeutic outcomes. Despite its rarity, documented instances intrigue researchers due to their departure from typical cancer trajectories. However, the underlying pathogenesis of this phenomenon remains incompletely understood. It highlights the complex interplay among the tumor microenvironment, host immune system, and tumor biology. Several theories have emerged to elucidate this occurrence, including hypotheses involving tissue necrosis from rapid growth, angiogenic inhibition and immune-mediated mechanisms,[3] some of which we discuss below as they pertain to RCC.

3.1. Immune mediated regression

Before TKIs and immunotherapy emerged, treatment choices for the primary tumor in mRCC had limited efficacy, and nephrectomy and metastasectomy were viable palliative options. The decision to perform cytoreductive nephrectomy was influenced, in part, by evidence of spontaneous regression in metastatic sites. A 1993 study examining 91 mRCC patients who underwent nephrectomy found that 4.4 % (4 out of 91) experienced complete resolution of all metastatic disease.[4] It is crucial to emphasize that a significant proportion of documented instances of spontaneous regression occur within the pulmonary system. Accumulating evidence underscores the immunologically vibrant milieu of the lungs,[5] highlighting the intricate interactions between adaptive and innate immune cell populations therein, which could have a potential role in spontaneous regression. Even with the emergence of interferon-based immunotherapy, randomized clinical trials have evidenced improved survival outcomes associated with cytoreductive nephrectomy in mRCC.[6] Despite the recent advent of TKIs and ICPIs, there remains a potential indication for cytoreductive nephrectomy in patients presenting with favorable performance status and restricted metastatic burden.

Numerous hypotheses have been posited to elucidate the marked survival benefit associated with cytoreductive nephrectomy. Transcriptomic analysis of RCC immune infiltrates sourced from The Cancer Genome Atlas (TCGA) database has unveiled that ccRCC exhibits the highest degree of total immune infiltration and T cell infiltration among 19 distinct cancer types.[7] This finding bolsters the hypothesis that RCC tumors serve as immunological reservoirs, sequestering antibodies and lymphocytes. Furthermore, RCC tumor cells have been demonstrated to produce cytokines with T cell inhibitory properties and express elevated levels of Fas ligand (FASL), which can trigger T cell apoptosis.[8] In vitro investigations have provided additional insights, revealing that monocytes exposed to conditioned media from RCC cell lines acquire a myeloid-derived suppressor cell phenotype, characterized by the inhibition of T cell-mediated anti-tumor immune responses and reduced responsiveness to ICPIs.[9] Most instances demonstrating spontaneous regression of metastatic lesions subsequent to nephrectomy predominantly manifest within the pulmonary system, and research highlights the immunologically vibrant landscape of the lungs and the sophisticated modulation of immune responses within this microenvironment.[5] This evidence supports the hypothesis of an immune-mediated mechanism underpinning the phenomenon of spontaneous regression following nephrectomy. Nevertheless, the relative rarity of this occurrence underscores the potential existence of undiscovered immune-mediated interactions, warranting further scientific scrutiny.

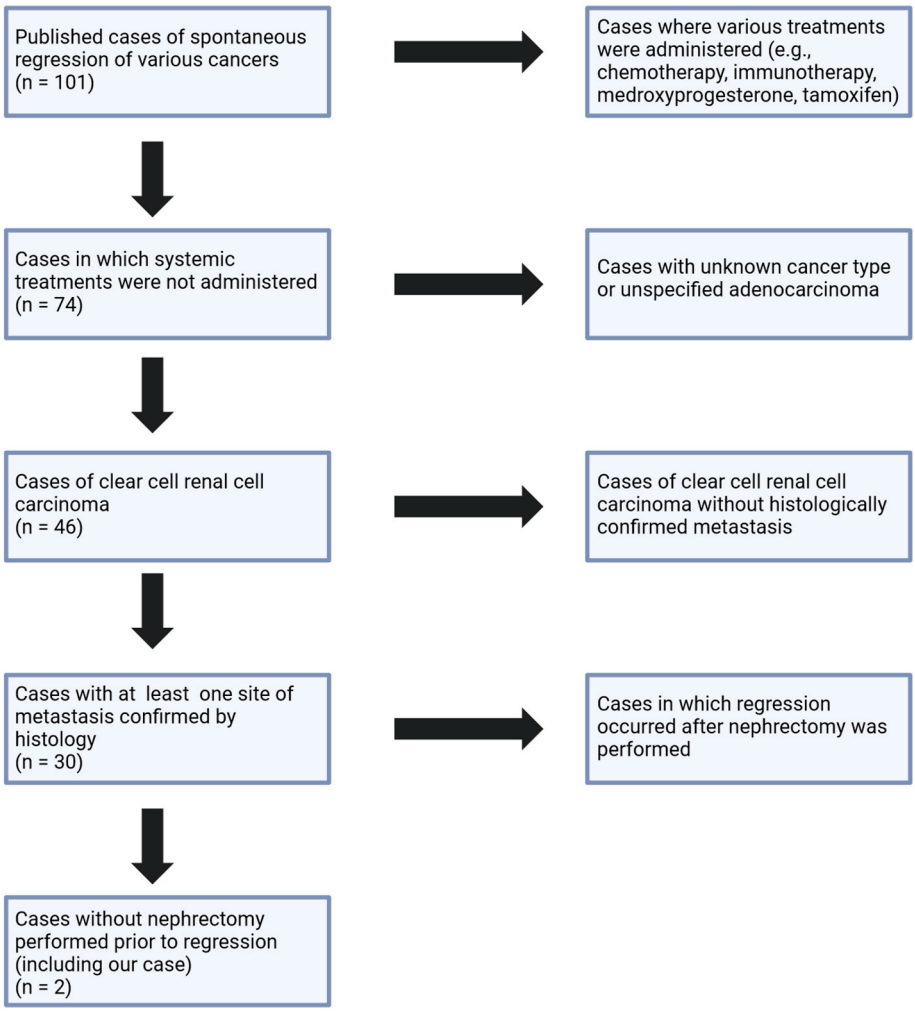

Fig. 3. Flow diagram of literature screening process. A comprehensive literature search for cases of spontaneous regression of malignancy was conducted utilizing the Ovid MEDLINE database, 1946 to September 18, 2023. Search parameters were "carcinoma, renal cell" AND "neoplasm regression, spontaneous". Publications were excluded if access methods were exhausted or if language barriers were present (Figure created in Biorender.com).

Table 1
Characteristics of reported cases of spontaneous regression of renal cell carcinoma.

Patient Characteristics	Total Cases (n = 30)
Age, years, median (range)	57 (37, 79)
Male sex, n (%)	22 (73.3)
Sites of metastasis, n (%)	
Lung/thoracic	20 (66.7)
Lymph nodes	8 (26.7)
Bone	2 (6.7)
Liver	2 (6.7)
Renal	2 (6.7)
Muscle	2 (6.7)
Complete Regression	19 (63.33 %)
Partial Regression	11 (36.67 %)
Number that received nephrectomy/resection of primary before regression, n (%)	28 (93.33 %)
Number that received no nephrectomy before regression, n (%)	2 (6.67 %)

3.2. Spontaneous tumor necrosis

Tumor necrosis (TN) resulting from cancer-directed treatments is often indicative of a favorable treatment response. Conversely, spontaneous TN tends to be linked with unfavorable clinical prognoses. Spontaneous TN is often associated with aggressive and rapidly proliferating tumors, where the rapid proliferation often results in tumor outgrowing its vascular supply.[10] This results in hypoxia and deprivation of vital nutrients leading to cytotoxic effects and cell death in the innermost regions.[11] Given limited apoptosis in cancer cells, cell death usually occurs by necrosis.[12] TN is often a hallmark of tumor aggressiveness and is associated with poor prognosis in RCC.[13] The poor prognosis associated with TN could be explained by necrosis leading to hematogenous spread of cancer cells, resulting in metastatic spread of the disease.[14] In a study involving 3009 surgically treated RCC patients at a single institution, TN emerged as a predictor of aggressive RCC phenotype[15] TN was detected in 30 % (n = 914) of analyzed RCC tumors, with its prevalence varying significantly across histologic subtypes. Notably, ccRCC tumors with TN (28 %) displayed more adverse pathologic features, such as high nuclear grade, advanced tumor stage, and increased rates of regional lymph node and distant metastatic involvement. Importantly, patients with ccRCC and TN were more likely to present with symptoms, including constitutional symptoms, highlighting the association between TN and tumor aggressiveness.

Tumor survival relies not only on adequate blood supply but also on angiogenesis, a vital aspect of tumor growth. While research highlights the potential role of cytokines such as tumor necrosis factor and transforming growth factor beta in inhibiting angiogenesis, their involvement in spontaneous regression remains undefined. The theory of angiogenesis inhibition posits that removing or destroying the primary tumor may reduce angiogenic factors, thus facilitating regression of secondary

Table 2
Specific cases of spontaneous regression of RCC.
Cases included in this analysis were confirmed to be RCC by biopsy to at least one metastasis and involved no systematic treatment prior to regression.

Author(s), Citation	Year	Invasive Procedures	Areas of Regression
Meinders, *Folia Med Neerl* v. 14, pp. 53–61.	1971	IV pyelography	Lung metastases
Downing & Levine, *Cancer* v. 35, pp. 1701–5.	1975	IV pyelogram, nephrectomy, resection of some lung nodules	Potentially some lung nodules (calcified tubercles when resected)
Freed et al., *J Urol* v. 118, pp. 538–42.	1977	Nephrectomy, resection of brain lesion, lower lobe of R lung, foot metastases, and buttock metastases	Most of remaining lung metastases
Freed et al., ibid.	1977	Thoracotomy and biopsy of lung lesion, IV pyelogram, nephrectomy	Pulmonary metastases
Freed et al., ibid.	1977	Biopsy of thigh lesion, pyelography, nephrectomy, disarticulation of LLE	Thigh lesion
Snow & Schellhammer, *Urology* v. 20, pp. 177–81.	1982	Oral cholecystogram, thoracotomy/resection of L 5th rib, removal of 3 lung nodules and attempt to remove others, IV pyelography, nephrectomy	Remaining lung nodules
Orbuch et al., *Medicina (B Aires)* v. 45, pp. 89–90.	1985	Nephrectomy	All but one lung metastasis
Ritchie et al., *J Urol* v. 140, pp. 596–7.	1988	Nephrectomy, lymph node dissection, liver biopsy	Liver metastasis
Davis et al., *Urology* v. 33, pp. 141–4.	1989	Cystoscopy, nephrectomy and para-aortic lymph node dissection, two transurethral resections of recurrent bladder tumors	Complete regression of lung metastases
de Riese et al., *Int Urol Nephrol* v. 23, pp. 13–25.	1991	Nephrectomy, paraaortic lymphadenectomy, splenectomy, drainage of pleural empyema	Both lung metastases
Vogelzang et al., *J Urol* v. 148, pp. 1247–8.	1992	Nephrectomy, aspiration of L lower lobe lesion	Complete regression of lung nodules
Marcus et al., *J Urol* v. 150, pp. 463–6.	1993	R radical nephrectomy with extensive pericaval lymphadenectomy	Complete regression of lung nodules
Marcus et al., ibid.	1993	Fine needle aspiration of a pulmonary nodule and renal mass, embolization of kidney with absolute ethanol and placement of arterial coil, nephrectomy	Complete regression of lung nodules
Kerbl & Pauer, *Aust NZ J Surg* v. 63, pp. 901–3.	1993	Thoracoscopy, biopsies to rib lesion, renal artery occlusion, nephrectomy	Partial regression of rib lesion
Vincent et al., *Cancer Immunol Immunether* v. 39, pp. 205–6.	1994	Cytopuncture of renal lesion, nephrectomy and removal of regional lymph nodes, sigmoidectomy	Lymph nodes
Elhilali et al., *BJU Int* v.86, pp. 613–8.	2000	Nephrectomy	Complete regression of three lung metastases, lymph nodes
Elhilali et al., ibid.	2000	Nephrectomy	Complete regression of four lung metastases
Elhilali et al., ibid.	2000	Nephrectomy	Partial regression of three lung metastases
Elhilali et al., ibid.	2000	Nephrectomy	Partial regression of four lung metastases, lymph nodes
Wyczolkowski et al., *Urol Int* v. 66, pp. 119–20.	2001	Nephrectomy, removal of periaortic lymph node mass, vaginal tumor resection	Complete regression of R liver lobe metastasis, partial regression of L liver lobe metastasis
Thoroddsen et al., *Scand J Urol Nephrol* v. 36, pp. 396–8.	2002	Nephrectomy	All but one lymph node
Sanchez-Ortiz et al., *J Urol* v. 170, pp. 178–9.	2003	Nephrectomy, fine needle aspiration and radiofrequency ablation of one of the metastases	Complete regression of lung metastases, loss of enhancement of renal metastasis
Nakajima et al., *BMC Cancer* v. 6, pp. 11.	2006	Radical nephrectomy, biopsy of sternal mass, partial resection of sternal bone	Sternal mass
Shields et al., *Case Rep Oncol* v. 13, pp. 1285–94.	2021	Nephrectomy, FNA of 2 noncalcified nodules of R lower lobe	Complete regression of lung nodules
Shields et al., ibid.	2021	Nephrectomy, endobronchial U/S fine needle aspiration of subcarinal lymph node	Complete regression of lymph node and pulmonary nodule
Shields et al., ibid.	2021	Nephrectomy, EBUS FNA of hilar lymph node	Complete regression of lymph node
Buchler et al., *Curr Oncol* v. 28, pp. 3403–7.	2021	Cryobiopsy of metastasis, nephrectomy	All lesions (lymph nodes, pulmonary)
Ahern et al. *Ann Thorac Surg* v. 112, pp. e249-51.	2021	Nephrectomy, wedge resection of R lobe metastasis	L lung metastasis
Freih-Fraih et al., *Rev Esp Patol* v. 55, pp. S69-73.	2022	Nephrectomy	Primary tumor
Current case	2023	Biopsy of primary and paraspinal mass	Partial regression of paraspinal muscle mass and lymph nodes

tumors, and this is postulated as the etiology of spontaneous tumor regression in previous case reports.[16–19]

3.3. Microbiome and spontaneous regression

Infections and the resulting release of inflammatory cytokines can have considerable immunomodulatory effects. The well-established influence of antibiotics on shaping the host microbiome, which in turn impacts the tumor microenvironment and subsequently affects responses to ICPIs, highlights their critical role in this mechanism. Several reports document instances where infections and fevers preceded spontaneous cancer regression.[20]

4. Conclusions

The notable disease progression observed in other metastatic sites among our cases suggests that spontaneous TN may be responsible for the partial regression of the paraspinal muscle mass, however interim improvement in clinical symptoms and absence of necrosis in the biopsy sample argues against this. While our patient did not undergo a nephrectomy, he underwent a diagnostic biopsy of the primary tumor and paraspinal muscle mass. An invasive procedure resulting in cellular injury can theoretically lead to exposure of intracellular neoantigens and a positive immune response. While the paraspinal muscle mass led to spontaneous regression of the metastatic lesion, there was a complete response following one cycle of ICPI, further raising the possibility of cellular injury-mediated immunomodulation. This underscores the potential interplay between TN, immune response, and treatment response, highlighting the need for further investigation into the

mechanisms underlying spontaneous regression in mRCC.

In conclusion, our case underscores the complexity and challenges in managing metastatic ccRCC. The patient's journey highlights the rarity of spontaneous regression in RCC and the uncertainties surrounding its mechanisms. While spontaneous regression offers a glimpse of hope, it is not a viable treatment strategy. Instead, appropriate medical interventions are crucial for optimizing patient outcomes. Further research is warranted to unravel the underlying processes driving spontaneous regression, potentially leading to innovative therapeutic approaches that could revolutionize the management of metastatic RCC.

CRediT authorship contribution statement

Anoushka Mullasseril: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Anh B. Lam:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Alekhya Mitta:** Writing – review & editing, Conceptualization. **Daniel Morton:** Writing – review & editing. **Andrew McIntosh:** Writing – review & editing, Conceptualization. **Sanjay Patel:** Writing – review & editing, Conceptualization. **Theresa Thai:** Data curation, Visualization, Writing – review & editing. **Anand Annan:** Data curation, Visualization, Writing – review & editing. **Adanma Ayanambakkam:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Ethics statement

Signed consent was obtained from the patient presented to publish potentially identifying information.

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Conflict of intertest

No author has any conflict of interest to declare.

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