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Case Series

Unusual sites of delayed metachronous metastases from renal cell carcinoma: a case series of five cases and review of literature

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ABSTRACT

Renal cell carcinoma (RCC) is the most common malignant tumour of the kidney, representing 3% of all adult malignancies. Among men it is the sixth most common cancer while among women it is the ninth most common cancer. The mainstay of treatment for localized RCC is surgical resection with curative intent. The aggressive and often insidious nature of RCC is reflected by high recurrence rates of upto 20-40% after nephrectomy. Most commonly encountered sites of recurrent metastases include the lung, followed by bone, liver, brain, and local recurrence. Atypical sites of delayed metastases of RCC, although rare, have been reported in literature. We present our series of five cases where delayed metastasis has occurred at atypical sites including right sartorius muscle, right atrium and ventricle, urinary bladder, shaft of tibia and distal phalanx of hand upto six years later from the time of initial curative treatment of primary. The metastatic lesions in sartorius muscle, right atrium and ventricle, urinary bladder and distal phalanx were primarily managed by metastatectomy while that in the tibial shaft was managed by palliative targeted therapy with tyrosine kinase inhibitors. The key takeaway from this case series is that any primary neoplastic lesion in a patient with history of RCC should be evaluated with histopathology before definitive intervention is undertaken keeping in mind the notorious tendency of RCC to cause delayed metachronous metastases at unusual sites. In presence of solitary metastatic lesions at resectable locations, curative treatment can be offered by metastatectomy.

Keywords: RCC, Delayed recurrence, Metastasis, Metachronous, Case report

INTRODUCTION

RCC is the most common malignant tumour of the kidney, representing 3% of all adult malignancies.[1] Among men it is the sixth most common cancer while among women it is the ninth most common cancer.[2] Surgical resection with curative intent is the cornerstone of treatment for localised RCC. However, the aggressive and insidious nature of RCC is reflected in the high recurrence rates after nephrectomy of upto 20 to 40%. Recurrences have been reported as late as 30 years after nephrectomy; however, 43% occur within the first year, 70% within the first two years, 80% within the first three years, and 93% within the first five years after curative resection. The most commonly encountered sites of recurrent metastases post treatment include the lung, followed by bone, liver, brain, and local recurrence. Atypical sites of delayed metastases of RCC, although rare, have also been reported in literature. We here present our series of five cases where delayed metastasis has occurred at atypical sites upto six years later from the time of surgery for RCC.

CASE SERIES

Case 1

A 48-year-old man presented with a non-painful, slowly progressive right thigh swelling that had been present for two years. The patient sought medical attention after

beginning to experience some difficulty walking. The right leg and thigh X-ray revealed soft tissue swelling and MRI confirmed the presence of a 13.6×4.3×3.2 cm lesion in the right sartorious muscle. On T1-weighted (T1W) imaging, it appeared heterogeneous and iso-hyperintense to muscle, whereas on T2-weighted (T2W) imaging, it appeared heterogeneous and hyperintense. No additional metastases were detected. The swelling was treated by radical excision. Histopathology revealed a diagnosis of metastatic clear cell RCC. This patient underwent radical nephrectomy eight years ago for a right-sided, stage 2 (T2aN0M0), Fuhrmann's grade III RCC. At the one-year follow-up, the patient is doing well (Figures 1 and 2).

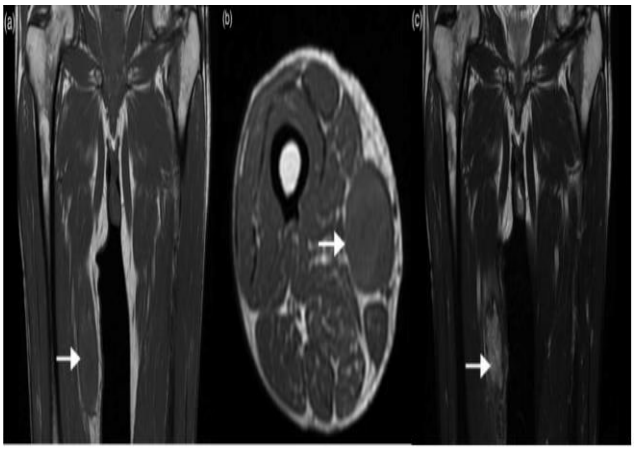

Figure 1: MRI of bilateral lower limb of iso to hyperintense lesion in the right sartorius muscle.

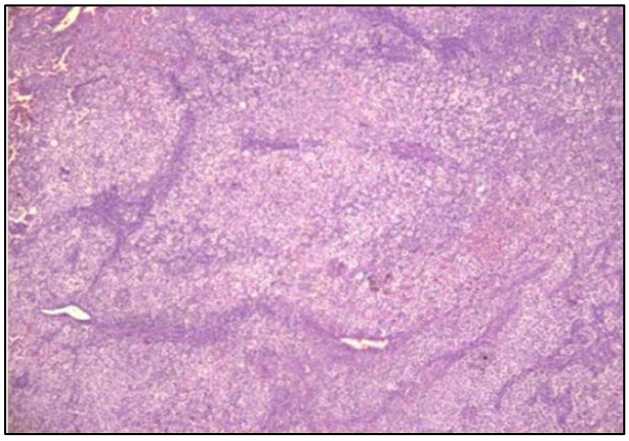

Figure 2: Microscopy of tissue sections suggestive of metastasis from clear cell RCC.

Case 2

A 45-year-old woman presented with dyspnea on exertion and palpitations to the cardiology department. Clinical examination revealed elevated jugular venous pressure and pedal oedema. Echocardiography was suggestive of a mass in the right atrium and ventricle. The chest and abdomen CT scan confirmed the presence of a single mass lesion in the right atrium and ventricle, without evidence of any IVC thrombus or other neoplastic lesion in the abdomen. Six years ago, she had undergone radical nephrectomy for left-sided stage 2 (T2bN0M0) papillary RCC (Type 2, Fuhrmann's grade III). Assuming that it was a solitary RCC metastasis, the patient underwent a metastatectomy under cardiopulmonary bypass. Histopathology was suggestive of metastatic papillary RCC. This patient was started on sunitinib as adjuvant therapy, but she developed a local recurrence six months post-surgery and died due to refractory cardiac failure (Figures 3-5).

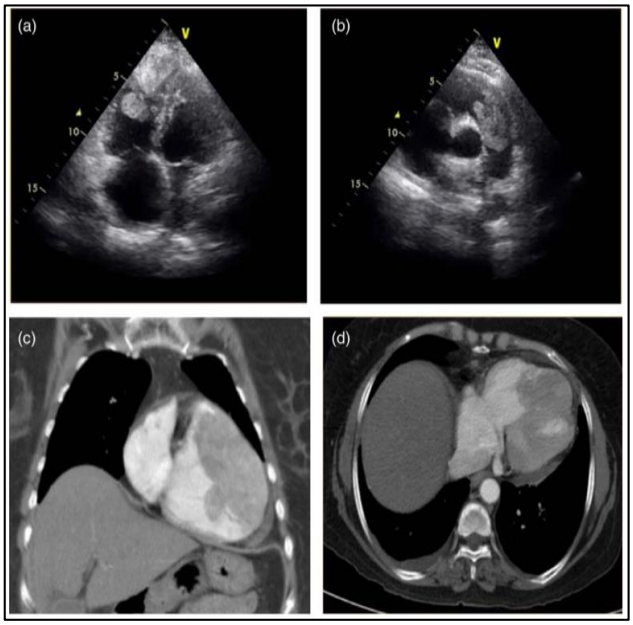

Figure 3 (A-D): Echocardiography showing solid mass lesion in the right atrium and ventricle. CT chest suggestive of heterogenously enhancing solid mass lesion in the right atrium and right ventricle.

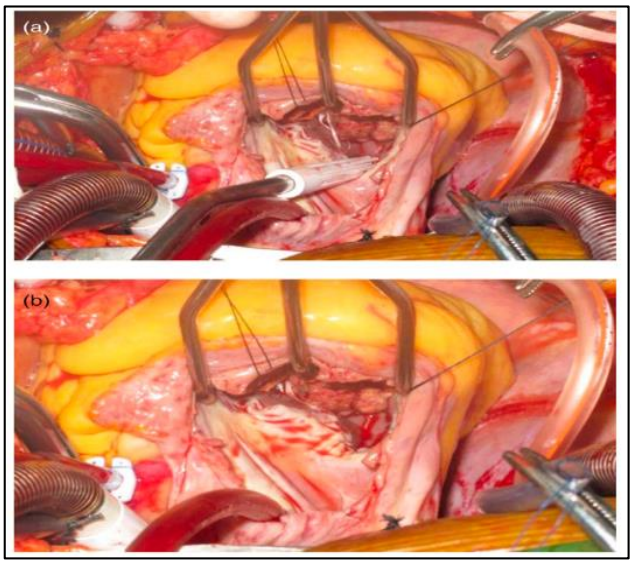

Figure 4 (A and B): Intra-op pictures of excision of lesion over cardiopulmonary bypass.

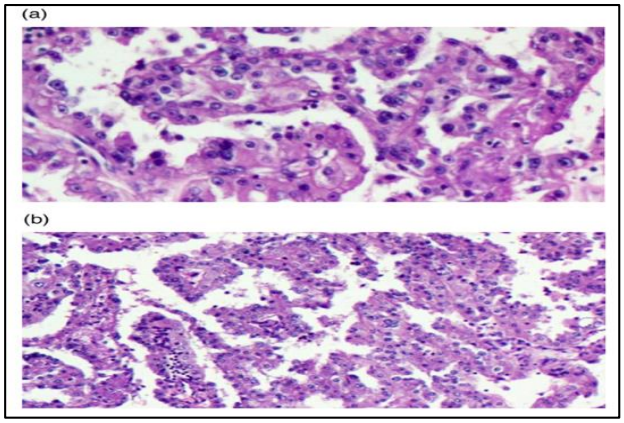

Figure 5 (A and B): Histopathological examination of excised tumor suggestive of metastasis from papillary RCC.

Case 3

A 64-year-old woman presented with a history of painless visible hematuria. Diagnostic workup with contrast-enhanced CT (CECT) revealed a 3×2.5×2 cm polypoidal enhancing mass over the posterior wall of urinary bladder. She had a complete transurethral resection of the bladder tumour (TURBT) done and histopathology was suggestive of metastatic clear-cell RCC. This patient underwent radical nephrectomy six years ago, and histopathology revealed stage 2 (T2bN0M0) Clear cell RCC (Fuhrmann's grade III). At 3 years of follow-up, the patient was doing well (Figures 6 and 7).

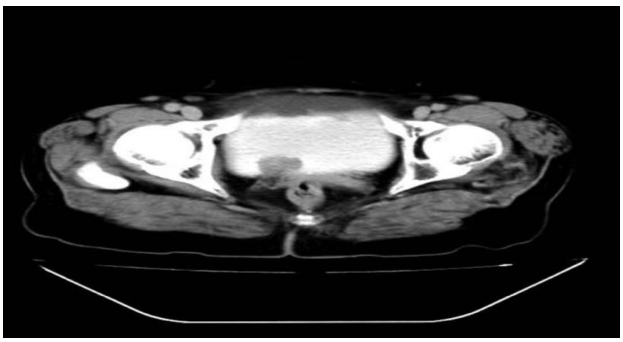

Figure 6: CT scan of polypoidal tumor arising from posterior bladder wall of size 3×2 cm.

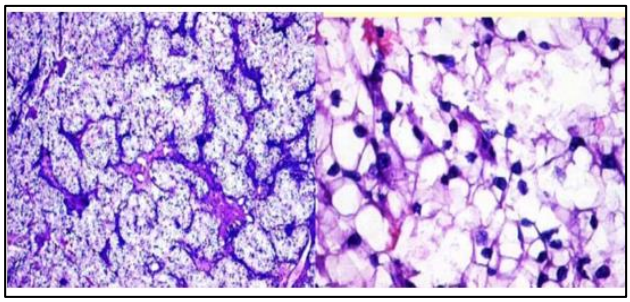

Figure 7 (A and B): Excised bladder tumor suggestive of metastasis from clear cell RCC

Case 4

A 58-year-old woman presented with pain in right leg for 2 months which was dull aching in nature and slowly progressive in intensity. X-Ray of right leg was indicative of well-defined lesion in the shaft of right tibia. MRI was suggestive of a 6.3×4.5×4.3 cm lesion in the shaft of right tibia which was hyperintense on T2-weighted (T2W) imaging. No evidence of other metastases could be found. She had undergone radical nephrectomy six years ago with histopathology suggestive of stage 2 Fuhrmann's grade II RCC (T2bN0M0). Core needle biopsy of the lesion was performed which was suggestive of metastases from clear cell RCC. Patient was started on palliative Sunitinib therapy and is doing well after 6 months of follow up.

Case 5

A 62-year-old woman presented with pain in right hand for 5 months which was dull aching in nature and slowly progressive in intensity. X-Ray of right hand was indicative of well-defined lesion in the right distal third phalanx. MRI was suggestive of a 6.3×4.5×4.3 cm lesion in the right distal third phalanx which was hyperintense on T2-weighted (T2W) imaging. No evidence of other metastases were found. She had history of radical nephrectomy done for RCC more than five years back. Digital phalanx amputation was done. Histopathology was suggestive of metastasis from clear cell RCC (Figure 8).

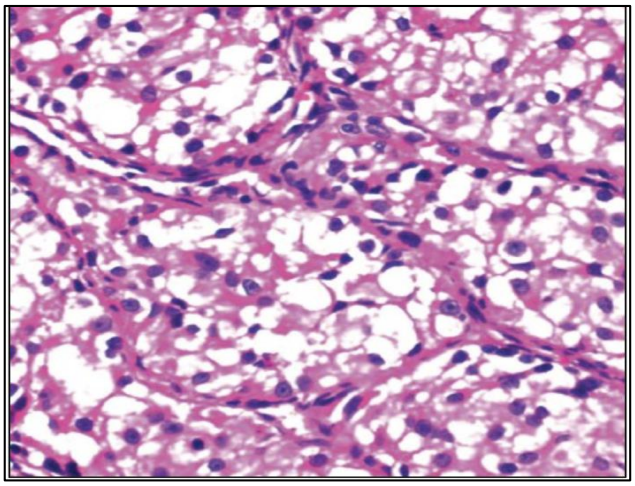

Figure 8: Microscopy of excised distal phalanx suggestive of metastasis from clear cell RCC.

DISCUSSION

A regular yearly follow up is advised following radical nephrectomy because the incidence of delayed metachronous metastatic lesions is 11% in patients who survive for at least 10 years after the first diagnosis.[3] After undergoing radical nephrectomy, 23.8 percent of patients (and 26.5% percent of those with T2 N0 M0)

develop metastatic RCC.[4] This risk is highest in the first three years following surgery. The initial pathological tumour stage can be used to guide surveillance protocol following radical nephrectomy. Only when there are accompanying symptoms, postoperative bone scans, bone plain films, and head CT scans are indicated. This cost-effective follow up protocol allows for the early identification of majority of cases of recurrent RCC following the radical nephrectomy for the localised disease.[5]

In RCC, isolated skeletal muscle metastasis is a rare occurrence.[6] When these isolated tumours are small and painless, they may pass unnoticed.[7] There are few published accounts of RCC metastasis to other skeletal muscles, such as gluteus maximus, trapezius, and psoas.[8-10] These metastatic lesions to skeletal muscles may be mistaken for benign primary soft-tissue tumours; therefore, a high degree of clinical suspicion is warranted if there is a past history of renal cancer. In the current case, the MRI for metastatic RCC was beneficial because MRI characteristics showing high-signal intensity on T1W and T2W sequence, would raise the suspicion for a malignant lesion, such as iso or hyperintense on T1W and heterogeneously hyperintense on T2W, as observed in the current case.[11] This signal intensity pattern appears to be characteristic of skeletal muscle metastasis of RCC. For confirmation of a suspected preoperative diagnosis, either an open or needle biopsy can be performed. In this instance, the histopathology obtained from an excisional biopsy confirmed the presence of metastatic RCC in the skeletal muscle. Surgical excision of metastatic RCC improves patient outcomes, and 5-year survival rates after surgery for a single metastatic focus range between 35 and 50%.[12] The patient was offered adjuvant targeted therapy but he could not comply to it due to financial constraints. One-year follow-up was uneventful.

There have also been numerous reports of a single late metastasis to multiple heart locations, including the left atrium and the right ventricle.[13,14] Cardiac metastases from RCC are uncommon and are typically caused by two routes. Micro dissemination via a venous haematogenous pathway is the most likely mechanism of metastasis in patients with a single metastatic lesion in the right heart and no involvement of the IVC.[15-17] The second route is via the lymphatic vessels of the thorax, followed by the nodes via the reversed lymphatic flow caused by metastasis.[17,18] Nkengurutse et al reported solitary metastatic lesion in left atrium developing 13 years after radical nephrectomy which was initially confused to be an atrial myxoma. Successful surgical resection was done and histopathology was suggestive of metastasis from RCC.[14] In our case, the patient had developed metastasis to the left atrium which was managed by surgical excision. Histopathology was suggestive of metastatic papillary RCC. Adjuvant immunotherapy was started but the patient expired due to refractory cardiac failure 6 months after surgery.

Isolated metastasis to urinary bladder is another rare metastatic recurrence from RCC that was encountered. Metastatic lesions to urinary bladder account for less than 2% of all bladder tumours with the most common primaries being malignant melanoma, gastric and breast cancers.[19] Dissemination to urinary bladder can be from a lymphatic route along the urothelial lining or by hematogenous route. Metastasis to urinary bladder is classified radiologically and morphologically into two types i.e., protuberant and diffuse type. Most of these lesions are protuberant type, with the most common symptom being of visible haematuria, as seen in our case.[20] Most of these lesions are amenable to endoscopic resection if diagnosed early. Cases where involvement of bladder is extensive, may require radical cystectomy.

Metastatic RCC can manifest as a single metastatic lesion or as an extensive systemic condition. A single metastatic lesion can eventually progress to widespread systemic disease.[21] Despite the advances in systemic therapy, the median survival of patients diagnosed with metastatic RCC is 6-12 months only with 5-year survival rate of 9%.[22] Patients with delayed isolated metastatic lesions have better prognosis than those with widespread metastases. Metastatic RCC remains highly resistant to chemotherapy, hormonal therapy and radiotherapy. Sunitinib is the most widely used immunotherapeutic agent in the initial treatment of metastatic clear cell RCC. Combination therapy including surgery and targeted therapy provides the best chance of palliation and cure. Table 1 summarises the rare sites of delayed metastases from RCC as reported in literature.

Table 1: **Summary of reports of rare sites of metastases from renal cell carcinoma.**

Study	Year	Site of metastasis	Latent period (Years)	Treatment	Outcome
Thadani et al (23)	2011	Pancreas	13	Distal pancreatectomy	Long term follow up unavailable
Ribeiro et al (24)	2019	Gall bladder & Pancreas	9	Laparoscopic cholecystectomy + Stereotactic radiotherapy for pancreatic nodule	Recurrence free at one year follow up
Nkengurutse et al (14)	2019	Left atrium	13	Excision	Stable and symptom free at 8 months follow up

Continued.

Study	Year	Site of metastasis	Latent period (Years)	Treatment	Outcome
Shahid et al (25)	2019	Orbital bone	4	None	Follow up unavailable
Rupal et al. (26)	2021	Right ventricle	10	Excision + pericardial patch placement	Recurrence free at 6 months follow up
Sakurai et al (27)	2022	Bilateral hilar lymph nodes + brain (occipital and temporal lobes)	20	Brain RT + combination immunotherapy (Avelumab + Axitinib)	Not available
Singla et al. (10)	2022	Jaw bone followed by scalp	15 months	Wide local excision + adjuvant combination immunotherapy (Axitinib and Nivolumab)	Successful excision and regression of residual lesion
	2022	Forearm	2	Wide local excision	Died after 3 years
	2022	Parotid	4	Targeted therapy + RT	Stable disease on short term follow up.
	2022	Skeletal muscle	4	Palliative sunitinib.	Follow up unavailable

CONCLUSION

We conclude that RCC, irrespective of stage and grade, can present with metachronous secondaries even many years after the curative treatment for primary lesion. A high degree of suspicion should be kept when patients present with a neoplastic lesion where history of treatment for RCC is present. Treatment of these metastatic sites depends on the site of metastasis and metastatic burden. In the presence of solitary metastatic lesions at resectable locations, curative treatment can be offered by metastatectomy.

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