Case Report

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Oncology Section

Very Late Solitary Metastasis for Renal Cell Carcinoma

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ABSTRACT

Renal Cell Carcinoma (RCC) is known for its recurrence in 50% of the patients. The highest risk for its recurrence is in the first three to five years after the diagnosis has been made. A recurrence after ten years of diagnosis is known to occur in 11% of the patients.

The natural history of RCC is unpredictable. An optimal surveillance protocol has been difficult to arrive at in view of its varied sites of recurrence and its varied time of recurrence. The sites of solitary recurrence can be anywhere in the body, but they have been found to be most commonly in the lung parenchyma (37%), bone (22%), liver (19%) and the brain (eight percent). It has been seen that early local treatment of the metastasis increases the survival. Bone metastasis is common but a disease free interval of more than 20 years has rarely been reported. We are describing here, a case of solitary bone metastasis which occurred very late, 32 years after the nephrectomy.

Key Words: Renal cell carcinoma, Late metastasis, Solitary metastasis

INTRODUCTION

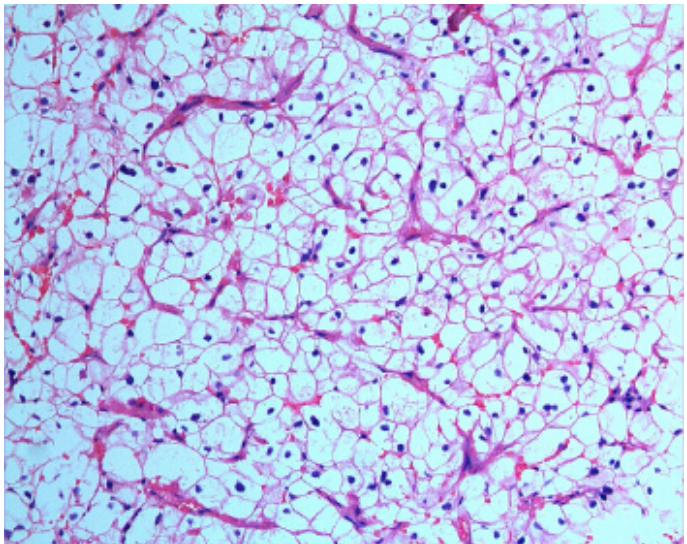
Renal Cell Carcinoma (RCC) accounts for two to three percent of all the cancers, and 33% of the patients who undergo resection for localized disease are prone for a local recurrence [1]. In patients with RCC, 20 to 25% have distant metastases at presentation and another 50% develop metastases during followup [2]. Among these, in 28% of the patients, there is recurrence in the first five years [3]. McNichols et al., reported a more than 10-year post surgery recurrence rate of 11% [4]. Only three patients have been reported so far with a clinical disease free interval of more than 30 years after nephrectomy [4, 5].

The natural history of RCC is unpredictable. The frequent sites for the solitary metastases of RCC include the lung parenchyma (37%), bone (22%), liver (19%) and the brain (eight percent) [6]. The other reported sites of the metastases include the rectum, adrenal gland, heart, thyroid, pancreas, IVC, duodenum, falciform ligament, psoas muscle, colon, vagina, skin, eye, spine, pelvis and the small bones of the hands and feet. The location, onset, clinical features and the prognosis of the metastasis from RCC are very variable. Bone metastasis is common in this setting, but a disease free interval of more than 20 years has rarely been reported [4]. We are describing here, a case of solitary metastasis which occurred 32 years after nephrectomy.

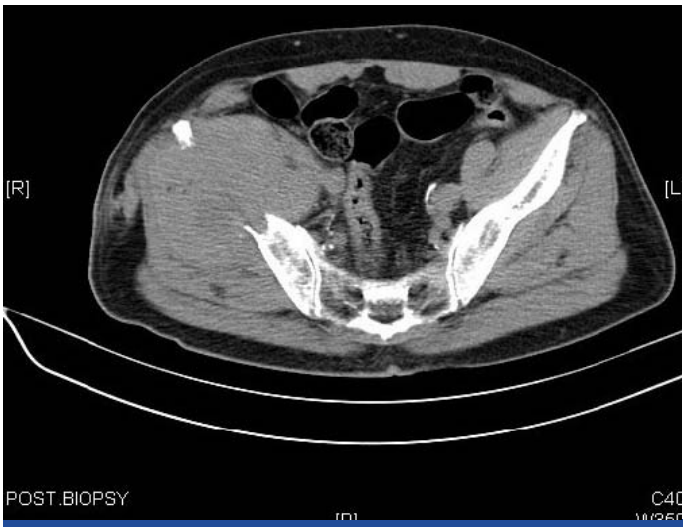
CASE PRESENTATION

A 76-six-year old gentleman presented in July 2006 with a three-month history of pain in the right groin region, which radiated to the right thigh. Thirty-two years earlier, in December 1974, he was evaluated for painless haematuria and he underwent a right nephrectomy to remove an upper pole mass which was adherent to the perinephric fat. Histopathology revealed polygonal cells with clear cytoplasm, well defined cytoplasmic borders, centrally placed small hyperchromatic nuclei and a small portion of cells having granular eosinophilic cytoplasm. The tumour cells were strongly positive for the epithelial membrane antigen (EMA). A diagnosis of clear cell renal cell carcinoma, Furhman's grade I was made. He did not receive any further treatment after the nephrectomy in 1974.

On examination in 2006, a 15×20cm palpable mass was found in the right iliac fossa, with limited movements of the right thigh, numbness and paresthaesia over the anterior thigh. MRI of the abdomen showed an expansile mass in the right iliac bone, which had no relationship with the renal bed. A CT guided biopsy of the lesion, as shown in [Table/Fig-1], reported it as metastatic renal cell carcinoma of the clear cell type [Table/Fig-2]. Bone scan showed an abnormal increased uptake in the right ilium with a central cold area. The rest of the skeleton showed no abnormality. In view of the co-morbid conditions (hypertension, diabetes and ischaemic



[Table/Fig-1]: H&E × 200. Ilium bone biopsy showed polygonal cells with clear cytoplasm and distinct cell borders with an intervening sinusoidal network.



[Table/Fig-2]: CT scan of pelvis showing large heterogenous expansile lytic lesion arising from the right iliac bone, measuring 8 × 6 cms

heart disease) and the patient's refusal of radical treatment, palliative radiotherapy (RT) to the right hemipelvis (30Gy in ten fractions) was given, followed by Zoledronic acid every four weeks. The patient declined any form of systemic therapy. The patient subsequently developed a brain metastasis for which a craniotomy and metastectomy were done, followed by whole brain RT alone in 2006. In June 2008, new lung metastasis was diagnosed on a chest X-ray and subsequently, the patient died in November 2008, following only supportive care.

DISCUSSION

Renal cell carcinoma can recur at anytime during the followup. Late recurrence is a feature of renal cell carcionoma. Late relapses and a prolonged disease free survival in the absence of systemic treatment and a rare spontaneous regression suggest that the host immune mechanisms are very important in regulating the tumour growth in RCC. The natural immune systems and the slow doubling times of the tumour may explain this type of late recurrence. In patients with a previous history of RCC, who present with apparently new lesions, metastatic RCC must be first ruled out [5].

John C Scatarige et al., listed out surgical stage, a large tumour with a venous tumour thrombus, regional lymph node metastasis, high Furhman's grade, and sarcomatoid tumour as the risk factors which are predictive of a recurrence of RCC [7]. Although metastasis to the bone is thought to be an indicator of a poor prognosis, it may be associated with a relatively prolonged survival. The factors that correlated with a longer survival were a long interval of more than 24 months of a recurrence free interval between the diagnosis of RCC and the formation of osseous metastasis and the absence of extra-osseous metastases [8].

If a solitary recurrence was detected, the best treatment was surgical excision, regardless of whether it was synchronous or metachronous [9]. The complete surgical resection of the metachronous metastases could result in a long term survival as compared to the situation in which there was no resection of the metastases [10].

Systemic therapy in either solitary or multiple metastatic RCC was found to have limited clinical benefits historically. Metastatic RCC showed a response rate of ten percent to immunotherapy with the use of interferons and/or interleukins and it has been shown to be refractory to chemotherapy with a response rate of four to eight percent [11].

Multiple targeted therapies have currently evolved as the result of a better understanding of the molecular pathways that are involved in clear cell carcinomas, that have shown significant clinical benefits. Tyrosine kinase inhibitors, Sorafenib, Sunitinib, and Pazopanib which target the vascular endothelial growth factor (VEGF) receptor have been shown to improve the progression free survival (PFS) (11 months for Sunitinib versus 5 months for cytokine therapy) of the patients, with an overall response rate which ranged from 47 to 57%. Temsirolimus and Everolimus, the agents that inhibit the serine-threonine kinase activity of the mammalian target of Rapamycin (mTOR), have shown benefit in metastatic RCC, with a PFS of 3.8 to 4.9 months versus 1.9 months that of placebo [11]. These agents are used as the second line of treatment when the disease progresses on VEGF targeted therapy. Bevacizumab, which is an antibody which is directed against VEGF, in combination with IFN, provides substantial response rates and an increased progression free survival as compared to those which are provided by IFN alone (10.2 months PFS versus 5.4 months) and it has been approved by FDA as the first line of therapy [12].

Unresectable bone metastases and bulky metastases show a limited response to the systemic therapy and are hence treated frequently with palliative radiotherapy. A radiotherapy dose of 30 Gy in ten fractions can result in a significant response rate and in the relief of the local symptoms [2]. When immunotherapy or chemotherapy had been added concurrently with radiotherapy, the response had been better comparatively. Brinkmann et al have reported the synergetic antitumour effect of combined immunochemotherapy (ICT) and radiotherapy (RT) in the treatment of bone metastases or local recurrence from RCC as compared to ICT or RT alone [13]. Kerst et al reported a phase II study where Thalidomide, along with a continuous low dose IL2 was shown to be effective in metastatic RCC along with palliative radiotherapy to the affected bones [14].

Bisphosphonates like Zoledronic acid are shown to reduce the skeletal complications from RCC like fractures, hypercalcaemia and spinal cord compression and predominantly, osteolytic lesions [15].

CONCLUSION

The risk of recurrence of the tumour at as late as 30 or 40 years of age suggests that metastatic RCC must be first excluded when patients who had been treated earlier for RCC present with apparently new lesions. The location of the metastases and their clinical features, onset, evolution and prognosis is very variable in RCC. The knowledge of the atypical sites of the metastases with RCC can lead us to an earlier diagnosis and treatment. An optimal surveillance protocol has been difficult to arrive at in view of the varied sites of recurrence and the varied times of the recurrence. Surgery should be offered as the first treatment of choice for the solitary metastasis from RCC, since it has been seen to increase the overall survival. When surgery is not feasible, local treatment with palliative radiotherapy, followed by systemic treatment, may be beneficial.

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