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Case Report

A Case of Toe Metastasis in a Von Hippel Lindau Disease Patient with Renal Cell Carcinoma

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Abstract

Von-Hippel-Lindau (VHL) disease is an inherited disease classically presenting with multi-organ tumorigenesis. Common tumors include hemangioblastomas, renal cell carcinoma, and pheochromocytoma. Metastasis to the bone, in particular, is common in VHL patients with existing renal lesions. However, bone acrometastasis, defined as a skeletal metastasis distal to the elbow or knee, is a much rarer occurrence. We present a unique case of bony acrometastasis in a 44-year-old woman with known VHL disease presenting with toe pain and swelling. This report highlights the evolving role of cytoreductive nephrectomy and amputation in the management of acrometastasis secondary to metastatic Renal Cell Carcinoma (RCC).

Keywords: Von hippel lindau; Renal cell carcinoma; Cytoreductive nephrectomy; Toe amputation

Introduction

The lifetime risk for renal cell carcinoma in the setting of VHL is greater than 70% and is a frequent cause of mortality in this patient population [1]. Protocols for the management of metastatic RCC are under continued investigation. The current standard of care is radical nephrectomy with either neoadjuvant or adjuvant chemotherapy. Here, we report a unique case in which acrometastasis to the second toe was the initial manifestation of metastatic RCC. We discuss the role of neoadjuvant chemotherapy, cytoreductive nephrectomy, and toe amputation in the management of this condition.

Case Presentation

A 44-year-old woman presented to our institution with right second toe pain after trying to remove a "fungal" growth. On examination, the toe had "beefy bleeding under the nail bed" but the patient was otherwise well-appearing. She had a past medical history significant for a pathologic variant VHL mutation found 20 years ago. She additionally had a family medical history of renal cancer in both her brother and uncle. She had not received regular VHL screening in the 5 years prior to her admission. The patient was initially managed with antibiotics and cleared for discharge. Excisional lesional biopsy confirmed a diagnosis of metastatic RCC.

Staging CT of the abdomen demonstrated multiple hepatic, pancreatic, and retroperitoneal cysts and masses. Imaging was most notable for a large heterogeneously enhancing right renal mass (Figure 1). Subsequent imaging studies of the chest and brain were unremarkable. Additionally, urine catecholamine testing for pheochromocytoma was negative.

Based on the patient's burden of disease, it was determined that she was a good candidate for the CytoKik trial which involves a course of Cabozantinib and Nivolumab followed by radical nephrectomy. The patient was able to successfully complete 3 cycles of CytoKik before stopping cabozantinib due to increasingly adverse physical reactions and elevated transaminases. Follow-up imaging 4 months after starting the CytoKIK trial and 6 months from original presentation demonstrated overall regression of metastatic disease with the exception of increased enhancement of a hepatic lesion and increased size of a left adrenal lesion (Figure 2). The patient then underwent right radical nephrectomy and was subsequently started on adjuvant chemotherapy with Pembrolizumab and Axitinib.

During the Cytokik course, the patient noticed re growth of the right second toe lesion. Vascular surgery was consulted for management of the recurrence. Given that the lesion was a biopsy-proven and recurrent metastatic site, further local excision was ruled out in favor of amputation. The patient tolerated the procedure well with no complications.

By 9 months from initial presentation, the patient's hepatic lesions and adrenal metastasis were noted to have enlarged. Therefore, she was transitioned to Lenvatinib/ Everolimus. Subsequent imaging initially demonstrated overall stability of metastatic disease with the exception of an interval increase in hepatic metastatic foci. However, imaging a month later demonstrated bilateral pulmonary masses, thoracic lymphadenopathy, a lytic lesion of the L1 vertebra, and further increases in the metastatic burden in the liver and retroperitoneum. She was therefore started on Belzutifan. Unfortunately, the patient began to decompensate clinically. After requiring several admissions, including two for hypercalcemia, and after a trial of Ipilimumab with Nivolumab, she was transitioned to hospice care. She died at 15 months from initial presentation.

Discussion

In the early 2000's, Cytoreductive Nephrectomy (CN) was

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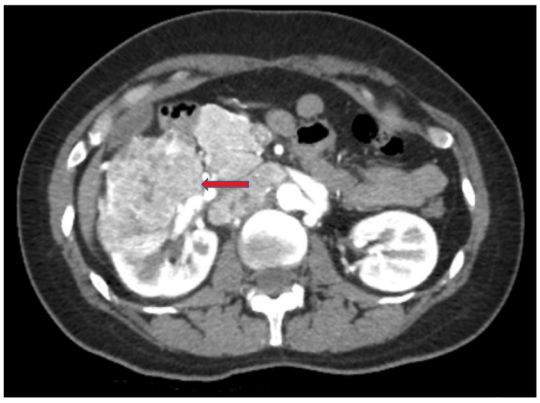

Figure 1: Staging axial CT of the abdomen and pelvis. A large heterogeneously enhancing right renal mass with cystic and necrotic spaces consistent with clear cell renal cell carcinoma.

established as the standard of care for metastatic RCC. At the time, systemic chemotherapeutic agents were largely interferon-based [2]. Resection of significant portions of renal parenchyma by CN was necessitated by the less-than-optimal regression of metastatic disease in response to systemic chemotherapy, with less than 5% of patients achieving a complete response [3]. However, in the modern-era, interferon-agents have largely been replaced by newer therapies such as immunotherapy and tyrosine-kinase inhibitors, exemplified by nivolumab and cabozantinib respectively. In the setting of metastatic RCC, such therapies have modestly improved efficacy, with up to 10% of patients achieving a complete response [4]. These improved response rates call into question the choice of radical cytoreductive nephrectomy in the surgical management of mRCC over the more conservative partial nephrectomy.

The decision to pursue radical cytoreductive nephrectomy in our patient was contingent on her response to the combined immunotherapy trial. Had a dramatic reduction in metastatic disease been observed, partial nephrectomy might have been considered. However, given her limited response to immunotherapy, radical nephrectomy was advised. The patient tolerated the procedure well with a postoperative course complicated only by persistent left elbow pain on exertion. In general, low complete response rates to modern chemotherapeutic agents suggest that many cases of metastatic RCC will continue to be managed with radical rather than partial nephrectomy.

In the setting of RCC, metastasis is the norm rather than the exception with up to 30% of RCC patients presenting with existing metastases and another 30% progressing to mRCC after nephrectomy for local RCC. Common metastatic sites include the lungs, lymph nodes, proximal bone, liver, and adrenal glands [4]. In the management of metastatic RCC, surgical resection is the gold standard in extending life expectancy. Without resection, the 5-year survival rate for metastatic RCC is less than 20%. On the other hand, in patients undergoing complete metastatectomy, the 5-year survival is nearly 50% with over 20% of patients remaining free of disease at last follow-up [5]. While the rarity of acrometastasis, especially in the setting of RCC, precludes large-scale clinical investigations on surgical management, it follows from the clear survival benefit of metastatectomy that surgical amputation of distal bony lesions is a necessary intervention in this small subgroup of patients.

In summary, we report a case in which an unusual metastasis to the distal bone presented as the initial diagnostic sign of metastatic RCC. This case details an unusual presentation for RCC in VHL and illustrates the role for aggressive surgical intervention in the treatment protocols for primary and metastatic foci.

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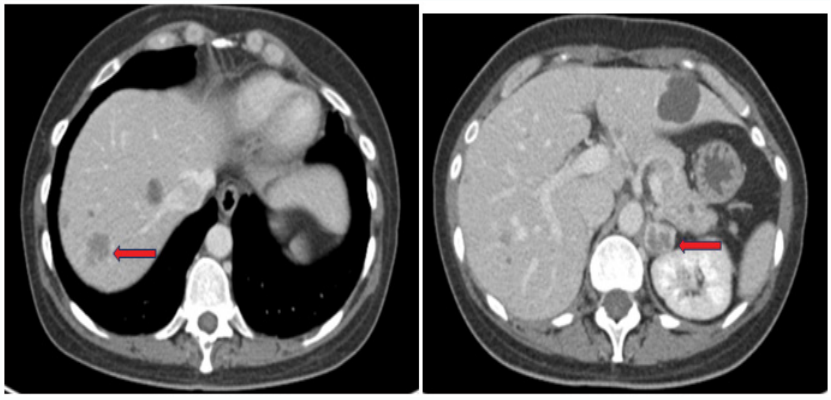

Figure 2: Restaging Axial CT of abdomen and pelvis demonstrating interval increase in size of hepatic (left panel) and adrenal masses (right panel).