CASE REPORT

Metastatic renal cell carcinoma mimicking diverticulitis in a patient with chronic lymphocytic leukaemia

S M Hwang,¹ J M Kuyava,² J P Grande,³ K M Swetz²

¹Mayo Medical School, Rochester, Minnesota, USA

²Section of Palliative Medicine, Mayo Clinic, Rochester, Minnesota, USA

³Department of Pathology, Mayo Clinic, Rochester, Minnesota, USA

Correspondence to

Dr K M Swetz, swetz.keith@mayo.edu

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SUMMARY

We present an unusual case of metastatic renal cell carcinoma (RCC) mimicking diverticulitis in a 76-year-old man with a 16-year history of chronic lymphocytic leukaemia (CLL) and a 2 cm left renal mass. The patient presented with severe abdominal pain and lower gastrointestinal bleeding with anticoagulation from recent pulmonary embolism. His clinical course was troubled by recurrent hospitalisations and complications that delayed investigations and potential treatments. Radiographic findings revealed stable CLL, mild sigmoid diverticulitis and a small renal mass. Small renal masses (less than 4 cm) are considered low risk for metastasising and are, thus, often observed or ablated, rather than resected. Furthermore, gastrointestinal metastases from RCC are rare. This case adds new perspective to the unpredictable nature of RCC and how synchronous malignancies may be masked in patients with long-standing CLL.

BACKGROUND

Renal cell carcinoma (RCC) confers an unpredictable prognosis due to variable behaviour by histological subtypes, lack of early warning signs, propensity to metastasise and historical resistance to treatment.¹ RCC is 1 of the 10 most common cancers in men and women. It occurs twice as frequently in males, with peak presentation in the sixth and seventh decades.² RCC can present with a classic triad of symptoms: haematuria, pain and a palpable mass in the abdomen or flank region. However, less than 10% of patients actually present with these symptoms.^{3–4} Consequently, 25–30% of patients with RCC have metastases at time of diagnosis, most often involving the lungs (75%), lymph nodes (36%), bone (20%) and liver (18%).⁵ Median survival rate for patients with metastatic RCC varies by prognostic factors;⁶ however, median overall survival has been estimated at 13 months, and 5-year survival is estimated at less than 10%.⁷ Nevertheless, RCC treatment has dramatically evolved in the past two decades with the use of immunotherapy and molecularly targeted therapy.^{8–9} Interleukin 2 and interferon α 2b were initially used with some success but were also associated with significant toxicity.⁷ Recently, the use of tyrosine kinase inhibitors (eg, pazopanib and sunitinib) and mammalian target of rapamycin (mTOR) inhibitors (eg, everolimus and temsirolimus) have shown improved prognosis and tolerability, and an increased survival for many patients.^{8–10}

This case report challenges the current recommendations for renal mass evaluation as our patient suffered from widely metastatic RCC from a solitary 2.1 cm left renal mass. This case was additionally complicated as his presenting symptoms were atypical abdominal pain and lower gastrointestinal (GI) bleeding. His long-standing chronic lymphocytic leukaemia (CLL) added additional complexity to this already perplexing case.

CASE PRESENTATION

The patient was a 76-year-old man with a medical history of long-standing B-cell CLL/small lymphocytic lymphoma and recent pulmonary embolism for which he was anticoagulated with warfarin. His case began when he presented to the emergency room with crampy lower abdominal pain and haematochezia. CT scan of the abdomen and pelvis revealed acute diverticulitis. An actively bleeding sigmoid diverticulum was treated endoscopically with epinephrine injection. Biopsies of small colonic polyps revealed a tubular adenoma with low-grade dysplasia and an inflammatory fibroid polyp. Anticoagulation was discontinued due to bleeding and an inferior vena cava filter was placed. He was discharged on levofloxacin and metronidazole for the diverticulitis.

Two weeks later, the patient was seen in the outpatient clinic after completing the antibiotics medication. He was feeling better. Warfarin was resumed for an additional 2 months. Since the diverticulitis was considered complicated, an elective sigmoid resection was recommended once anticoagulation was completed. Other issues noted during this follow-up included prostatic hypertrophy with an elevated prostatic specific antigen (23.5 μ g/L), a 4.7 cm abdominal aortic aneurysm, and a 2.1 cm mixed solid and cystic left kidney mass concerning for RCC (figure 1). Given the small size and lack of apparent symptoms, observation of the renal mass was recommended. Plans were made to proceed with partial nephrectomy versus open ablation along with prostate biopsy during the eventual sigmoid resection.

During the following weeks, the patient suffered a rapid clinical decline. He was evaluated in the emergency room on a weekly basis due to progressive, unrelenting abdominal pain. An extensive evaluation ruled out recurrent diverticulitis, prostatitis and mesenteric ischaemia. He was treated with an aggressive bowel regimen for suspected opioid-associated constipation. Although imaging

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Figure 1 CT scan at the level of the kidneys. Note large renal cyst on right kidney (red arrow) and the 2.1 cm partially cystic and solid mass on the left kidney (yellow arrow). Prominent periaortic lymphadenopathy is also present (white lines).

did not show progressive stranding or inflammatory changes, given his previous improvement with antibiotics, the patient was treated for recurrent diverticulitis. Opioids were required for pain management; however, his abdominal pain worsened and responded less to increasing opioids.

INVESTIGATIONS

The patient's initial complete blood count revealed a low haemoglobin of 95 g/L, haematocrit of 27.7%, erythrocyte count of $2.87 \times 10^{12}/L$, platelet count of $138 \times 10^9/L$ and a total leucocyte count of $6.1 \times 10^9/L$ with 84% lymphocytes. Prothrombin time was 20.2 s. Electrolytes and liver function enzymes were within normal limits.

Previous bone marrow biopsy was positive for B-cell CLL/small lymphocytic lymphoma. Fluorescence in situ hybridisation done, during the patient's worsening abdominal pain, revealed B-cell CLL with λ light chain restricted. This was consistent with his prior diagnosis and was not suggestive of transformation to a higher grade lymphoma.

On initial CT imaging, there was stranding in the descending/sigmoid colonic junction suggestive of diverticulitis. Diffuse lymphadenopathy was noted in the peripancreatic, retroperitoneal, periaortic, right inguinal and bilateral iliac regions. This was consistent with his known CLL. Prostate hypertrophy and left renal mass were noted.

MRI of the thoracic spine demonstrated diffuse, patchy abnormal marrow signal throughout the vertebral bodies. This was again consistent with known CLL. Soft tissue mass in the left posterior mediastinum, ventral to T4-T7, was suspicious for adenopathy. Biopsy of the vertebra or lymph nodes was considered but ultimately not pursued due to the anticoagulation, planned sigmoidectomy and strong clinical suspicion that these findings were consistent with his long-standing CLL.

DIFFERENTIAL DIAGNOSIS

Owing to the many medical issues, including diverticulitis, GI bleeding, CLL and left renal mass, the aetiology of the patient's abdominal pain was considered multifactorial. On review from haematology, it was believed that his CLL was quiescent and there was no suggestion of a Richter's transformation. Therefore, the diffuse lymphadenopathy was unlikely to be causing his abdominal pain. The left renal mass was worrisome for RCC; however, it was small. Since renal masses less than 4 cm rarely metastasise, his 2 cm left renal mass was not

considered a contributor to his pain. The abdominal aortic aneurysm was stable.

Some of the pain was believed to be from recurrent diverticulitis or possible urinary retention due to his enlarged prostate. While opioids alleviated the pain to some degree, these worsened the constipation which was strongly suspected to be a major factor of the patient's pain.

When his abdominal pain failed to respond to an aggressive bowel regimen, antibiotics and opioids, the differential diagnosis broadened to include partial bowel obstruction, metastatic prostate cancer, pancreatitis, osteoporotic vertebral compression fracture, parasitic small bowel infection and acquired C1 esterase inhibitor deficiency. However, his abdominal X-ray was consistently negative for perforation, bowel obstruction or new compression fracture. His laboratory studies remained unchanged.

TREATMENT

Treatment and advanced investigational options for the abdominal pain were limited by the multitude of comorbidities and his worsening clinical status. First, anticoagulation for recent pulmonary embolism postponed potential interventions, such as prostate biopsy, partial nephrectomy or tumour ablation, and sigmoid resection. If these interventions had been completed, a definitive diagnosis might have been realised. Second, while the abdominal pain persisted, the peritoneal signs, fever, leucocytosis (aside from chronic lymphocytosis) and uncontrollable bleeding were lacking; thus, emergent surgical intervention was not pursued. A third factor that limited physicians' ability to further investigate the patient's abdominal pain was the pain itself. Despite the efforts of numerous providers (primary and subspecialists), his pain remained poorly controlled. The patient was unable to proceed with the planned outpatient evaluations as he was frequently in the emergency department or hospital due to pain. His condition declined so rapidly that the planned interventions never took place.

OUTCOME AND FOLLOW-UP

The patient died within 3 months of his initial presentation. Postmortem examination revealed the immediate cause of death as sepsis and multiorgan failure in the setting of diffusely metastatic RCC. On autopsy, the left kidney mass measured 1.8 cm and had concordant pathology with metastatic lesions (mixed cell type RCC, clear cell and pleomorphic predetermined; [figure 2A–C](#)). RCC metastases were found in the lung, liver, spleen, pancreas, lymph nodes, vertebrae ([figure 3A, B](#)) and rectosigmoid colon ([figure 4](#)).

DISCUSSION

This case reviews an atypical presentation of metastatic RCC. The incidence of RCC had been steadily increasing since the 1980s, primarily due to advancement in imaging and earlier detection.^{11 12} A recent study revealed that the rising incidence of RCC is largely attributable to a 2.5-fold increase in the detection of small renal masses (less than 4 cm). These small masses are presumably early-stage disease and can be cured with ablation or resection.¹² Several studies also demonstrate that renal mass size alone does not predict likelihood of metastatic disease.^{13–15} Nevertheless, to date, the clinical decision to undergo observation or surgical intervention of a renal mass still depends heavily on tumour size.¹¹ Whether the tumour subtype (ie, clear cell, papillary, chromophobe, etc) affects prognosis of RCC remains controversial, but independent studies from Mayo Clinic and Memorial Sloan-Kettering Cancer Institute both found clear cell RCC to have a worse overall survival rate.^{16 17}

Figure 2 Gross anatomical and histological images of the mixed cell type renal cell carcinoma in patient presented. (A) Gross image of kidneys. The red arrow shows a large cyst on the lower pole of the right kidney and correlates with the red arrow on figure 1. Yellow arrow shows the 1.8 cm cancerous mass on the lower pole of the left kidney. (B) A $\times 40$ magnification of the renal mass. The black arrow shows normal kidney including a glomerulus for comparison. The adjacent area marked 'CC' shows grade 2 renal cell carcinoma, clear cell type, with characteristic haemorrhage (H). (C) A $\times 400$ magnification of renal parenchyma involved by mixed type renal cell carcinoma: grade 4 de-differentiated type (black arrow) and grade 2 clear cell type (yellow arrow).

The patient's renal mass, at autopsy, showed mixed clear cell histology with areas of higher grade de-differentiation. The fact that increased and earlier detection has not altered the mortality

Figure 3 Gross anatomical and histological images of renal cell carcinoma metastases in the vertebral column. (A) Several tumour nodules on the vertebral bodies (indicated by black arrows). (B) Normal bone tissue (B) invaded by high-grade de-differentiated renal cell carcinoma (black arrow). Samples taken from the patient's liver, lungs and spleen (not shown) demonstrated the same morphology of wide metastases by the de-differentiated type renal cell carcinoma.

rate for RCC suggests reconsideration of the evaluation and management of small renal masses.^{13–15}

This case is unique in that a small renal mass (2.1 cm on CT; 1.8 cm on autopsy) caused widely metastatic disease. On imaging, the diffuse osseous and lymphatic metastases appeared consistent with the patient's known CLL; however, on autopsy, these were found to be extensive RCC metastases. A recent study conducted at five international institutions showed that among 1208 patients who presented with a small renal mass (less than 4 cm), 88% were malignant and only 5–8% were metastatic.¹⁴ To this end, two similar studies supported a more aggressive approach to evaluating suspicious renal masses, even those as small as 2.5 cm.^{13 15} The patient's case further emphasises that tumour size alone is not a reliable prognostic tool.

Figure 4 Gross anatomical image of the colon showing multiple diverticula (indicated by black arrows) leading to concern about the diagnosis of diverticulitis.

Based on RCC's unpredictable nature and propensity to metastasise, there is growing evidence to support investigating small renal masses.¹⁸

RCC has a diverse and unpredictable range of clinical manifestations and can present insidiously with non-specific abdominal pain.¹⁹ Metastases to the GI tract are a rare complication seen predominantly in advanced stages of disease with multiple organ involvement.²⁰ GI bleeding as the presenting symptom of RCC has been rarely documented.²¹ When present, bleeding is often limited to the upper GI tract and is typically associated with recurrent cases of RCC rather than initial presentation.^{5 19 22–24} There are less than 10 reported cases of metastatic RCC presenting with lower GI bleeding.^{18 21 25 26} One case report described a 74-year-old man who presented with sudden onset haematochezia. CT revealed a large mass on the left kidney invading into the sigmoid colon.²⁵ Another case report observed both upper and lower bleeding in a 78-year-old man with a 52-pack-year smoking history whose duodenal biopsy led to the finding of a 7 cm renal mass.²⁷ Similarly, all previously published cases of primary RCC presenting as lower GI bleeding had three similarities: (1) RCC was widely metastatic at the time of diagnosis, (2) the renal tumour was large (>4 cm) and (3) surgical intervention was considered or performed for palliation. The patient's case differed from these previously reported cases in that the primary renal tumour was small.

Surgical interventions for symptom palliation in widely metastatic RCC have been reported in several studies.^{23 24 28} In the setting of GI bleeding, surgery is recommended not only as a life-saving procedure for haemostasis, but also as a method to minimise the risk of obstruction and provide relief of pain.^{23 28} Surgical resection of the affected bowel can prevent the tumour from developing collateral vessels and subsequently decreases the risk of recurrent GI bleeding.²⁴ Unfortunately for the patient, anticoagulation and the uncertainty surrounding the aetiology of his pain prevented earlier surgical intervention. In the setting of diverticulitis, it is common to wait for active, non-perforated disease to stabilise with antibiotics prior to surgical resection. If it was known that his abdominal pain and GI bleeding were due to diffusely metastatic RCC, a palliative surgery might have been offered. However, based on the burden of metastatic disease discovered on autopsy, along with his poor functional status, it is highly unlikely that partial bowel resection would have altered the outcome in this case.

The patient's pain brought him to the emergency department numerous times. During his many hospitalisations, over 50 staff physicians reviewed his case. Extensive, appropriate and iterative evaluations did not reveal a cause for his pain. We now know,

based on the autopsy results, his pain was from widely metastatic RCC with visceral and osseous metastases.

Despite numerous consultations, emergency department visits and hospitalisations, the patient suffered at the end of his life. His family understandably still struggles when they think back to that time and recall the pain he experienced. His physicians worked diligently to find an explanation for his symptoms, but answers were few. When confronted with incredibly challenging cases like the present case, the uncertainty surrounding the case should be clearly and continuously communicated to patients and families in order to minimise their suffering.

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Learning points

- ▶ Renal cell carcinoma (RCC) presenting as a small mass (<4 cm) can be widely metastatic.
- ▶ Small RCC can metastasise to the gastrointestinal (GI) tract and cause severe abdominal pain and GI bleeding.
- ▶ In patients with uncontrolled pain, worsening functional status and stable chronic lymphocytic leukaemia, a new malignancy should be considered.
- ▶ When faced with complicated cases with unclear diagnoses and uncontrolled symptoms, it is recommended and appropriate to convey uncertainty to patients and their families, and to validate their concerns.

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