

Case Report

Appendiceal neuroendocrine tumour association in a patient with a large sarcomatoid renal cell carcinoma

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ABSTRACT

Renal cell carcinoma (RCC) can develop into sarcomatoid differentiation which demonstrates aggressive biological behavior evident by the rapid progression of the tumour with multiple metastases. Though the appendiceal neuroendocrine tumour (NET) has a good prognosis, the prognosis can be worse when associated with the sarcomatoid RCC (sRCC). A 45-year-old female patient presented to the emergency department with a 2-month history of worsening right upper abdominal pain, nausea, vomiting, and significant weight loss. Computed tomography (CT) revealed heterogeneously enhancing solid cystic mass lesions arising from a lower pole of the right kidney with a tumour thrombus involving the entire right renal vein and extending into the inferior vena cava (IVC). The patient underwent radical nephrectomy and appendectomy and was managed conservatively due to the poor prognosis. After four weeks, she presented with severe right upper abdominal pain, and Magnetic resonance imaging (MRI) indicated a possible liver metastasis and tumour necrosis. In three weeks, the patient died of respiratory failure following multiple organ dysfunction syndrome (MODS). This case report outlines a presentation of sRCC with biologically aggressive disease progression and a rare association with appendiceal NET. CT, MRI, and PET scans can be helpful in the diagnosis and monitoring of disease progression. Early identification of the sRCC and appendiceal NET will contribute to better outcomes of the disease and complications. The prognostic elements and similar genetic patterns of sRCC and appendiceal NET would be of great clinical interest.

Keywords: Vascular surgery, Renal cell carcinoma, Neuroendocrine tumor

INTRODUCTION

Sarcomatoid renal cell carcinoma (sRCC) is defined as renal cell carcinoma (RCC) with a foci of malignant sarcomatoid spindle cells which can associate with any histological type of RCC.¹ Sarcomatoid transformation of RCC presents in 4% of all RCCs, can appear in most histological subcategories of RCC and is associated with a poor prognosis.² The prognosis of sarcomatoid RCC is terminal, with 60-80% presenting with late stage of disease.² The median survival of these patients ranges between 6-13 months based on the percentage of sarcomatoid differentiation on histology.²

For patients with localised, non-sarcomatoid RCCs, nephrectomy is the primary treatment option with a favourable prognosis.² Unfortunately, a paucity of effective treatment evidence exists for metastatic sRCCs, with palliation considered the mainstay of management.²

NETs arising in the tubular gastrointestinal tract, lung, and genitourinary tract were initially referred to as 'carcinoids' because they seemed morphologically different and clinically less aggressive than the more common gastrointestinal tract adenocarcinomas.³ The incidence of appendiceal NETs is 3 to 9 per 1000 appendectomy surgeries, accounting for one NET in every

150 to 300 appendectomies approximately.⁴ Well-differentiated appendiceal NETs have shown a good prognosis without distant metastasis, but the prognosis can be worse when associated with sRCC.⁵ There is no prior literature examining metastatic sRCC and its association with appendiceal carcinoid neuroendocrine tumours. In this case report, we outlined a case of a 45-year-old female with an sRCC and an incidental appendiceal carcinoid NET.

CASE REPORT

Presentation and patient background

A 45-year-old female patient presented to the emergency department with a 2-month history of worsening right upper abdominal pain, nausea, vomiting, and significant weight loss. The patient was on irbesartan for hypertension for six months. Her mother was diagnosed with breast and uterine cancer. She was a non-smoker and had social alcohol consumption. Her blood results showed normocytic anaemia and slightly high potassium and serum creatinine levels. The patient was referred to a gastroenterologist who performed a gastroscopy which returned nil significant findings. She underwent a CT scan to investigate abdominal pain. Computed tomography (CT) abdomen and pelvis revealed a heterogeneously enhancing solid cystic mass lesion arising from a lower pole of the right kidney, completely obliterating the right kidney measuring 169×135×157 mm. There is a tumour thrombus involving the entire right renal vein extending into the IVC, causing approximately 50% narrowing of the IVC. The occlusion of the renal vein is causing extensive varices surrounding this mass. A small retroperitoneal nodule posterosuperior to the kidney revealed a retroperitoneal metastatic deposit. An appendiceal mass of 10 mm was noted. Positron emission tomography (PET) revealed fluorine-18 fluoro-2-deoxyglucose (FDG) avidity in the right kidney and the appendix, and no other areas of metastasis were demonstrated. Subsequently, the patient underwent a radical nephrectomy, cavotomy, thrombectomy, and appendectomy.

Pathology findings of the right nephrectomy showed a grade four 180 mm clear cell type renal cell carcinoma in some areas a spindle type morphology in keeping with sarcomatoid transformation, with a tumour thrombus being detected within the renal vein. Tumour necrosis was identified (30%). Tumour infiltration into the perirenal fat, renal sinus, renal vein, and renal pelvis was noted. Lymphovascular invasion was recorded (pT3aNx).

The appendix pathology results showed a grade 1 well-differentiated neuroendocrine carcinoid tumour 1, measured at 46 mm in its maximum dimension involving the distal half and the tip of the appendix. Tumour perforation into the visceral peritoneum with perineural invasion was identified. It was negative for lymphovascular invasion. All resected margins were free of tumour involvement. One lymph node showed a

metastatic neuroendocrine tumour (pT4N1). Considering the metastatic disease and poor outcome from the sarcomatous RCC, palliative measures were offered to the patient after a multidisciplinary team discussion.

After four weeks, she presented with severe right upper abdominal pain, and MRI indicated a possible liver metastasis and tumour necrosis. In three weeks, the patient died of respiratory failure following multiple organ dysfunction syndrome (MODS).

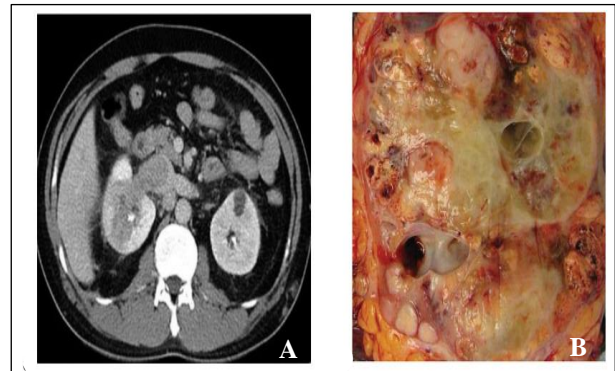


Figure 1: (a) CT abdomen showing a right renal mass protruding into the inferior vena cava; and (b) gross specimen of sRCC.

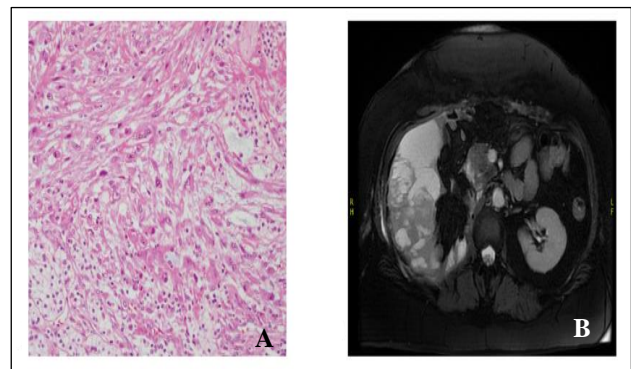


Figure 2: (a) Histology shows the spindle cell of the sarcomatoid carcinoma invade the renal tissue; and (b) MRI abdomen shows the recurrent sRCC after right nephrectomy.

DISCUSSION

RCC is gradually increasing in prevalence worldwide, albeit the observed mortality rates have stabilised in response to greater therapeutic developments in high gross domestic product countries.⁶ Sarcomatoid transformation of RCCs describes the process in which a part of the tumour changes into a high-grade undifferentiated segment that is characterised by the spindle cells within tumour cells.⁷⁻⁹ Sarcomatoid transformation of the RCC warrants its poor prognosis due to rapid local extension and distant metastasis.⁷ Prognostic factors of sRCC should

highlight the tumour size, sarcomatoid components, pathological stage, necrosis of the tumour, and genetic factors.⁸

The poor prognosis of sarcomatoid cellular transformation has prompted research into factors of sRCC with reduced prognosis.⁷ The degree of sarcomatization is demonstrated to be associated with significantly decreased prognosis in patients without distant metastasis and greater than 25% sarcomatoid cells.¹⁰ In patients with distant metastasis, this yields as the dominant determinant of mortality.¹⁰

Malignancies with greater TNM scoring, with distant metastasis to the lungs and bone are predictors of increased mortality.² The traditional progression of RCC starts by being renally confined (stage 1), invading into perinephric fat and Gerota's fascia (stage 2), lymphovascular penetration into the ipsilateral renal vein and adjacent nodes, and distally metastasising into tissue.¹¹ Patients with stage 1 RCC have a 5-year survival of 88%, decreasing ultimately to 15% in patients with Stage 4 RCC.¹¹

Tumour necrosis in areas with sarcomatoid transformation is associated with poorer prognoses.² The size of the tumour may also contribute to the overall prognosis of the tumour, which can be an independent predictive factor of cancer-specific mortality.^{8,12}

Almost eighty percent of patients who underwent curative nephrectomy for localised SRCC complicate with recurrence within 5-26 months.⁸ Radical nephrectomy is important for complete resection of the bulky tumour before starting the systemic chemotherapy.¹³ Management of metastatic sRCC is primarily aimed at prolonging longevity rather than aiming for complete remission.¹⁴ Whilst only effective in 33% of patients with sRCC, the use of interferon and/or interleukin-2 immunotherapy is demonstrated to increase median survival from seven months to nineteen months.¹⁴ Likewise, combination chemotherapy agents using doxorubicin and gemcitabine were shown to improve prognosis by five months in 40% of sRCC cases.¹⁴ The overall futility of the existing treatment regimens for patients with metastatic sRCC highlights the need for clinical developments in this area.¹⁵

Within the appendix, 70% of neuroendocrine neoplasms are well-differentiated NETs with the remainder being high-grade neuroendocrine carcinomas.^{16,17} The prognosis of appendicular NETs is generally favourable compared to other neoplasms in the appendix.

Five-year appendiceal NET-specific survival rates range from 100% for tumour sizes <2 cm without regional nodal or distant metastasis down to 32% in patients with demonstrated distant metastases.¹⁸ As observed in the case report, the prognosis can be worsened when patients have a concurrent metastatic sarcomatoid RCC and appendiceal NET. For appendiceal NETs <1 cm, a simple

appendectomy is curative.¹⁹ For tumours 1-2 cm, appendectomy followed by five years of postoperative follow-up is recommended.^{5,19}

Patients may be indicated for a right hemicolectomy with oncological resection margins within three months of their appendectomy if warranted based on increased tumour size (>2 cm), basal appendicular positioning of the tumour, caecal infiltration, involvement of surgical margins on appendectomy, mesentery invasion, involvement of mesoappendiceal lymph node and presence of goblet cells.^{19,20}

Secondary gastrointestinal (GI) malignancies are recognised metastatic sites of RCCs.^{21,22} Histologically, GI secondary metastases are more prevalent in patients with papillary-subtype and chromophobe-subtype RCCs rather than clear cell subtypes.²²

SRCC and appendiceal NETs show similar genetic patterns as they both involve recurrent mutations of TP53.^{8,23} The Von Hippel-Lindau (VHL) gene is associated with 35% of sRCC cases, and the VHL gene is related to gastroenteropancreatic NETs though it is mainly involved with pancreatic NETs.^{8,24}

CONCLUSION

This case report outlined a 45-year-old female patient with an appendiceal NET associated with a severely aggressive metastatic sarcomatoid renal cell carcinoma causing mortality. To the best of our knowledge, this is the first report of an appendiceal NET associated with a large sRCC. The prognosis of appendiceal NET can be worse when associated with sarcomatoid RCC. This case report probes discussion into the genetic patterns between gastroenteropancreatic NETs and sRCCs. Further genetic studies are needed to identify the similarities between SRCC and appendiceal NETs genetics, which will aid in determining the reasons for concurrent tumours.

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