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Case Report

Renal cell carcinoma presenting as painless jaundice and unintentional weight loss

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Abstract: Painless jaundice and unexplained weight loss is an exceedingly rare presentation for renal cell carcinoma (RCC). Such a presentation is more typical of a hepatocellular pathology. Stauffer syndrome is a paraneoplastic syndrome seen in RCC and is characterized by deranged hepatic enzymes and in association with fever, fatigue and weight loss. These symptoms typically resolve following nephrectomy. The predominant picture of this syndrome is that of an anicteric patient. Here we report the case of a 48 year old man who presented with a 3 week history of painless jaundice, malaise, anorexia and unintentional weight loss of 10 kilograms. Imaging revealed a solid right renal mass measuring 11 cm × 11 cm × 14 cm. There were also findings consistent with the presence of an inferior vena cava thrombosis and multiple pulmonary lesions. Biopsy confirmed the pulmonary lesions as metastatic clear cell renal carcinoma. Following multi-disciplinary discussion, cytoreductive nephrectomy was recommended to the patient, however multiple paraneoplastic syndromes subsequently developed and the patient experienced hypertension, severe coagulopathy and hypercalcaemia. Subsequently, the patient opted for supportive and palliative care. The patient died 2 weeks after initial presentation. Paraneoplastic syndromes associated with RCC are often underdiagnosed due to their variety and often non-specific nature. Paraneoplastic syndromes may lead to patient presentation, where they often suggest advanced or metastatic disease, and those caring for such patients should remain vigilant as further syndromes may complicate patient care.

Keywords: Stauffer syndrome, painless jaundice, paraneoplastic syndrome, RCC

Introduction

Paraneoplastic cholestatic jaundice as the presenting complaint for RCC is an exceedingly rare but important presentation [1]. While tumours often cause cholestasis by obstructing the main bile duct or widespread hepatic metastases, it is more rarely due to a paraneoplastic manifestation. Such rare presentations have previously been documented in lymphoproliferative diseases such as Hodgkin's disease and non-Hodgkin's lymphoma [2, 3].

RCC is a relatively common tumor, that has a somewhat variable clinical course, unpredictable metastatic pattern, and can present with a variety of non-renal manifestations [4]. The classic triad of flank pain, haematuria and a flank mass is now a relatively uncommon presentation (~6-10%), and is more suggestive of locally advanced or metastatic disease [5].

Here we report the case of a patient who presented with painless jaundice, and was subsequently diagnosed with a renal cell carcinoma, without any hepatic metastases.

Case report

A 48 year old previously healthy gentleman was referred for further assessment by his general practitioner as he had presented with a three week history of painless jaundice, malaise, anorexia and unintentional weight loss of 10 kilograms. Upon further questioning he described pale stools and dark urine, without any pruritis or abdominal discomfort. There was a family history of malignancy: his father having died with oesophageal carcinoma, and his brother having recently being diagnosed with lung carcinoma. He had smoked 20 cigarettes daily for over 20 years. None of his close contacts had been ill nor had he travelled abroad recently.

On examination, he was afebrile, with a normal blood pressure and pulse rate. He was clinically jaundiced with discolouration of his skin, sclera

and oral mucosa. His abdomen was soft and non-tender with no palpable masses or organomegaly present. His physical examination was otherwise unremarkable.

His laboratory investigations revealed deranged liver and renal function tests: Bilirubin 36 [laboratory reference range (rr) 0-21 μmol/L], alkaline phosphatase (ALP) 612 [rr 40-129 IU/L], ALT 135 [rr 0-41 IU/L], gamma glutamyl-transferase (GGT) 614 [rr 10-71 IU/L], Urea 8.2 [rr 2.8-8.1 mmol/L], Creatinine 121 [rr 59-104 μmol/L]. His full blood count revealed he was also anaemic with a haemoglobin of 10.2 g/dL [rr 13.5-18.0 g/dL].

Ultrasonography of the abdomen revealed a solid right renal mass measuring 11 cm × 11 cm × 14 cm. There were also findings consistent with the presence of an inferior vena cava thrombosis. A computed tomography of the brain, thorax abdomen and pelvis obtained after oral and intravenous contrast material administration confirmed the ultrasound findings, and further characterised the renal tumour. It also identified significant thrombus in the inferior vena cava and multiple pulmonary lesions consistent with metastasis but did not identify any other lesions or pathology.

Following histological confirmation of the pulmonary lesions as metastatic clear cell renal carcinoma, and multidisciplinary meeting discussion, the initial management plan was to perform a cytoreductive nephrectomy and commence chemotherapy.

There was a rapid deterioration in this gentleman's condition, with the onset of hypertension, prior to significant bilateral lower limb oedema, and later, coagulopathy manifest as a severe upper gastrointestinal bleed and haemodynamic instability, which required transfusion with red cell concentrate and fresh frozen plasma. This was accompanied by hypercalcaemia, and an acute deterioration in renal function.

Subsequently, the patient opted for supportive and palliative care. The patient died 2 weeks after initial presentation.

Discussion

The incidence of renal cell cancer (RCC) is rising globally, and accounts for 2.4% of all newly diagnosed cancer cases. According to GLOBOCAN data, RCC is the 12th most common malignancy worldwide, and the highest incidence is seen in the United States and Eastern Europe. In the US, RCC is the 6th leading malignant condition among men and the 9th among women [6]. The 5-year survival rate for early stage RCC is up to 93%, however for patients who present with metastases, this rate is ~12%.

RCC has a somewhat variable clinical course, unpredictable metastatic pattern and can present with a variety of non-renal manifestations [4]. The classic triad of flank pain, haematuria and a flank mass is now a relatively uncommon presentation (~6-10%), and is more suggestive of locally advanced or metastatic disease [5]. The increased use of computed tomography (CT) and magnetic resonance imaging (MRI) has led to the more widespread detection of incidental renal tumours, and many patients with RCC now have few or no symptoms at the time of diagnosis.

The presentation of a patient with RCC spans a spectrum: from a lanthanic disease process, to diverse, non-specific, and obscure symptoms such as flank pain, lower extremity oedema, ascites or hepatic dysfunction and scrotal varicocoele. Because of the multiple initial signs, symptoms and many metabolic manifestations, it has become known as the "internist's tumour" [7].

The reported incidence of paraneoplastic syndromes at presentation in patients diagnosed with RCC, ranges from 10-68% [8], with some common and many lesser known syndromes (see **Table 1**). Excess production of certain cytokines or hormones can result in fever, hypercalcaemia, or hepatic dysfunction in the absence of liver metastasis. Anaemia, or less frequently thrombocytosis can also occur in patients with RCC. The aetiology of many of these paraneoplastic syndromes is poorly understood.

The hepatic abnormalities which can occur in RCC, include elevation of alkaline phosphatase and bilirubin, hypoalbuminaemia, prolonged prothrombin time and hypergammaglobulinaemia. These abnormalities help characterise Stauffer syndrome which tends to occur in association with fever, fatigue, weight loss and

Table 1. Paraneoplastic syndromes in renal cell carcinoma

Hormonally mediated	Non-hormonally mediated
Hypercalcaemia	Amyloidosis
Hypertension	Non-metastatic hepatic dysfunction
Polycythaemia	Coagulopathy
Anaemia	Vasculopathy
Galactorrhoea	Nephropathy
Cushing's syndrome	Neuromyopathies
Alterations in glucose metabolism	Prostaglandin elevation

Table 1 describes some of the more common paraneoplastic syndromes associated with Renal Cell Carcinoma. These broad descriptive categories include paraneoplastic motor neuron disease [20], as well as reports of bilateral diaphragmatic paralysis secondary to a paraneoplastic syndrome of RCC [21].

these typically resolve following nephrectomy. An anicteric patient with elevated hepatic cholestatic enzymes (alkaline phosphatase and gamma glutamyl-transferase) is the prevailing picture in this syndrome, with jaundice-as in this case-a relatively rare presenting complaint [1].

Dr. Maurice H. Stauffer first characterized a paraneoplastic syndrome of hepatic dysfunction in 5 patients with renal neoplasms in 1961, with the original name of 'nephrogenic hepatomegaly' [9]. In the initial publication, Stauffer outlines that all cases appeared to have chronic liver disease, with an enlarged liver and spleen, as well as abnormal ALP and prothrombin values. A review of 29 cases of Stauffer Syndrome revealed 15% had hyperbilirubinaemia, but none to the degree necessary to present with visible jaundice [10]. Over thirty years after Stauffer's report, Dr. Spyros P. Dourakis et al were first to characterize cholestatic jaundice as a paraneoplastic manifestation of RCC in 1997 [1]. In their description of 2 cases, and similar to this case, no clinical manifestations of RCC were detected prior to abdominal imaging. Two other cases of this "variant" of Stauffer Syndrome have subsequently been described in the literature [11, 12].

There is much debate and little consensus as to the pathogenesis of many of the para-neoplastic syndromes associated with RCC. This is also true of hepatic dysfunction seen in RCC. Some advocate that the hepatic abnormalities are not due to tumour infiltration of the liver or intrinsic liver disease; but are instead, a reflection of the presence of a para-neoplastic syndrome. Chang et al hypothesised that this may be due to overproduction of granulocyte-macrophage colony stimulating factor by the renal tumour [13]. Others have postulated that activation of the immune response occurs secondary to a neoplasm derived direct hepatotoxin [14]. Attempts to produce the syndrome in model systems have been unsuccessful. Regardless, of the pathogenesis, most para-neoplastic syndromes associated with localized RCC are definitively treated with nephrectomy [15], underscoring the importance of recognising such paraneoplastic syndromes, as well as early detection of the renal mass and early intervention.

Conclusion

Before the advent of advanced imaging techniques, less than 10% of renal tumours were diagnosed incidentally [16, 17]. Now, the rate of incidental diagnosis of renal masses is as high as 40% [18, 19]. While there has been much debate surrounding the use of advanced imaging, this case emphasizes the importance of judicious and timely access to advanced imaging, and identification of such symptoms as those of a para-neoplastic syndrome.

Disclosure of conflict of interest

None.

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