African Journal of Internal Medicine ISSN: 2326-7283 Vol. 2 (5), pp. 037-041, July, 2013. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Case Report

Successful right nephrectomy and left tumourectomy for sporadic bilateral synchronous renal cell carcinoma

A Murinello[1], P Guedes[1], AM Figueiredo[1], P Gomes[1], LA Monteiro[2], HS Damásio[1], NC Ribeiro[3], L Mota[4], A Carvalho[5], C Teiga[3], M Albergaria[3], A Serrano[1]

[1]Internal Medicine 1 Department, Hospital de Curry Cabral – Rua da Beneficência 8, 1069-166 Lisbon, Portugal.
[2] Urology Department, Hospital de Curry Cabral – Rua da Beneficência 8, 1069-166 Lisbon, Portugal.
[3] Radiology Department, Hospital de Curry Cabral – Rua da Beneficência 8, 1069-166 Lisbon, Portugal.
[4] Intensive Care Unit, Hospital de Curry Cabral – Rua da Beneficência 8, 1069-166 Lisbon, Portugal.
[5]Pathology Department, Hospital de Curry Cabral – Rua da Beneficência 8, 1069-166 Lisbon, Portugal.

Accepted 2 May, 2013

Renal cell carcinoma (RCC) is by far the most frequent type of kidney cancer, but synchronous bilateral neoplasms are rare, even more so in sporadic forms of RCC. An increasing amount of tumours are being found spuriously while small and before causing any symptoms, thus allowing less invasive surgery with potentially brighter outcomes. We report a 49-year-old Caucasian male who presented to the Emergency Department with a seven-day course of productive cough, worsening dyspnoea, and anorexia. He had no history of fever or any pain, and showed no abdominal or urinary complaints whatsoever. His physical exam was irrelevant apart from an enlarged liver, and kidney function tests were normal. Workup eventually revealed synchronous bilateral clear cell RCC and the patient underwent a successful total right nephrectomy with left tumourectomy. Two years on, he remains asymptomatic and with normal renal function. This case shows the seldom seen coexistence of sporadic RCC in both kidneys. We stress the fact that the patients frequently don't show any urinary symptoms, which can delay the correct diagnosis and hinder treatment. Tumours found on an early stage can be dealt with using less drastic measures that spare nephrons and elude, or at least postpone, definitive haemodialysis.

Key words: kidney cancer, sporadic bilateral synchronous renal cell carcinoma, clear cell renal cell carcinoma, guided percutaneous diagnostic kidney biopsy, nephron-sparing surgery.

INTRODUCTION

Renal Cell Carcinoma (RCC) accounts for 80-90% of primary malignant kidney cancer. RCC is not a single entity but consists of different types of tumours. There are two forms of RCC – sporadic or non-familial, and hereditary or familial. Bilateral cases are uncommon, occurring in 2-4% of RCC (Rashid S 2008). Hereditary RCC affects both kidneys more often than sporadic cases, where less than 2% of patients have bilateral neoplasms (Rashid S 2008). Paired organs such as kidneys have one feature in common – they are under the exact same carcinogenic influences, both genetic and environmental. The histopathology of non-familial RCC includes conventional clear cell renal cell carcinoma (CCRCC) in 70-80% of cases, papillary RCC (15%) and chromophobe RCC (5%), as well as several rarer tumors (Eble J 2004). Hereditary forms of RCC tend to be bilateral, multifocal in each kidney and occurring at younger age (Grimaldi G 1998). The most common inherited types of RCC are: autosomal-dominant hereditary CCRCC, renal cancer associated with von Hippel-Lindau disease involving the *VHL* gene (3p25.5) and hereditary papillary RCC (Grimaldi G 1998); another rare variant is the Birt-Hogg-Dubé syndrome. Remarkably, defects in the *VHL* gene also appear to be responsible for about 60% of sporadic clear cell carcinomas (Cohen H 2005). Sporadic bilateral RCC may present as synchronous or metachronous. Most authors regard it as synchronous if the second primary RCC develops within six months of the first, and asynchronous if thereafter (Klatte T 2007). Others define synchronicity as a period of up to one year from the first diagnosis

*Corresponding author. E-mail: amurinello@gmail.com, amurinello@iol.pt, antoniomurinello@yahoo.com.
Tel: +351 918626874, Fax: +351 217924304.

(Chen D 2011). Most do not consider that synchronous bilateral RCC reflects metastatic disease from one kidney to the other. Genetic analysis of the tumor is the only tool helpful in differencing metastatic disease from primary neoplasm (Klatte T 2007). Multifocality (existence of at least two RCC in the same kidney) is more frequent in hereditary and bilateral sporadic cases rather than unilateral, but in any event it does not appear to affect survival. The incidence of multifocal RCC, however, is probably under-reported since microscopic multifocality can be undetected during nephron-sparing surgery (Klatte T 2007). Nowadays RCC are often discovered incidentally on imaging studies done for different reasons. Finding a kidney mass implies rapid characterisation of the lesion, thereby increasing cure rate and patient survival (Rashid S 2008). Ultrasonography (US), computerised tomography (CT), magnetic resonance imaging (MRI) and guided percutaneous biopsy are useful means of diagnosing renal neoplasms. Nephron-sparing surgery is increasingly being used in smaller tumours that are identified earlier thanks to modern imaging methods (Rashid S 2008).

CLINICAL REPORT

A 49-year-old caucasian male waiter was admitted to our Emergency Department (ED) due to respiratory failure. During the previous week he had complained of increasing dyspnoea, productive cough with purulent sputum, anorexia and asthenia, along with depressive mood and refusal to eat and talk after a brother's suicide on the previous week. He denied any other symptoms. He was a heavy smoker (60 pack-years) and reported high alcoholic intake that stopped six years before when he was diagnosed with type 2 diabetes mellitus (T2DM), for which he did not regularly take the prescribed oral antidiabetic drugs. He had no history of arterial hypertension or dyslipidaemia. His father had died due to colon cancer and his mother was alive, suffering from T2DM. He had ten siblings – three brothers and six sisters, all alive, and the aforementioned dead brother – all without known diseases. On physical exam he was obese with a Body Mass Index (BMI) of 33kg/m^2, apyretic (axillary temperature 36.6ºC), tachypnoeic (respiratory rate 26bpm), tachycardic (heart rate 109bpm) and hypertensive (blood pressure [BP] 158/83mmHg). He showed lip cyanosis and muffled breath sounds with some inspiratory crackles at the lower third of his right hemithorax. Heart sounds were normal. A soft non-tender hepatomegaly (palpable 2cm below the costal margin) was detected. There was no splenomegaly and kidneys were not palpable. No abnormal masses were detected and there was no ascites. There was no lumbar abnormality. There was no jaundice, peripheral oedema or any other relevant finding. Fundus and neurological examination were both normal. Blood work revealed: haemoglobin 13.3g/dl, leucocytes 12.1x10^9/L, platelets 450x10^9/L; erythrocyte sedimentation rate 41mm, C-reactive protein 9.9mg/dl, lactate dehydrogenase 1101U/L; glucose 369mg/dl, HbA1c 10.3%; liver enzymes showed elevated aspartate aminotransferase (257U/L) and alanine aminotransferase (243U/L), but gamma-glutamyl transpeptidase, alkaline phosphatase and bilirubin were normal; cholesterol 179mg/dl, high-density lipoprotein 35mg/dl, low-density lipoprotein 140mg/dl, triglycerides 182mg/dl; kidney function was preserved – urea 32mg/dl, creatinine 0.6mg/dl and an estimated glomerular filtration rate (GFR) of 157ml/min (Cockcroft-Gault formula). No other relevant anomalies were disclosed. His arterial blood gas showed severe global respiratory failure (PaO_2 30.9mmHg and $PaCO_2$ 76.9mmHg) with respiratory acidaemia (pH 7.330). His bicarbonate level was appropriately high (32.1mmol/L); lactate (1.4mmol/L; N: 0.6-1.6) and anion gap (8.7mmol/L; N <12) were both normal. Sputum culture was negative for bacteria and *Mycobacteria*. Urinalysis revealed no haematuria, no leucocyturia and no proteinuria. Chest radiograph showed reinforced lower right bronchovascular markings, with no signs of consolidation or pleural effusion, and no images suggesting primary or secondary neoplasm. Tuberculin test was negative. The patient was immediately started on intravenous ceftriaxone (2g once daily) plus oral clarithromycin (500mg twice a day), and non-invasive ventilatory support (BiPAP) was initiated due to worsening respiratory failure. He stayed in the ED for two days and his respiratory status improved steadily, after which he was transferred to our Internal Medicine service, although remaining on nocturnal BiPAP. Sputum culture had not been done in the ED and was of questionable use when we first evaluated the patient, 48 hours into antibiotic therapy, so we opted to process samples for *Mycobacteria* only, which turned out negative (Ziehl-Neelsen and Löwenstein-Jensen). Antidepressant therapy with venlafaxine was initiated, after which the patient began to recover and resumed eating. Hepatitis viruses B and C serology and VIH serology were negative. An abdominal US was performed because of his elevated aminotransferases, but revealed only diffuse steatosis. Unexpectedly though, it did show a 4-cm nodular hypoechogenic lesion in the right kidney. This prompted a contrast-enhanced helical abdominal CT that disclosed a hypodense solid mass in the right kidney, with some calcifications and mild enhancing in late images, causing distortion of the intra-renal urinary excretory tree and invading the renal sinus (Figure 1A), and a smaller hypodense solid mass in the left kidney without apparent invasion of the renal sinus. Planning nephron-sparing surgery we completed imaging studies with an abdominal MRI that revealed nodules in both kidneys with weak signal in T1-weighed sequences (Figures 1B and 2) and heterogeneous images in T2-weighed sequences, varying between areas of hypo- and

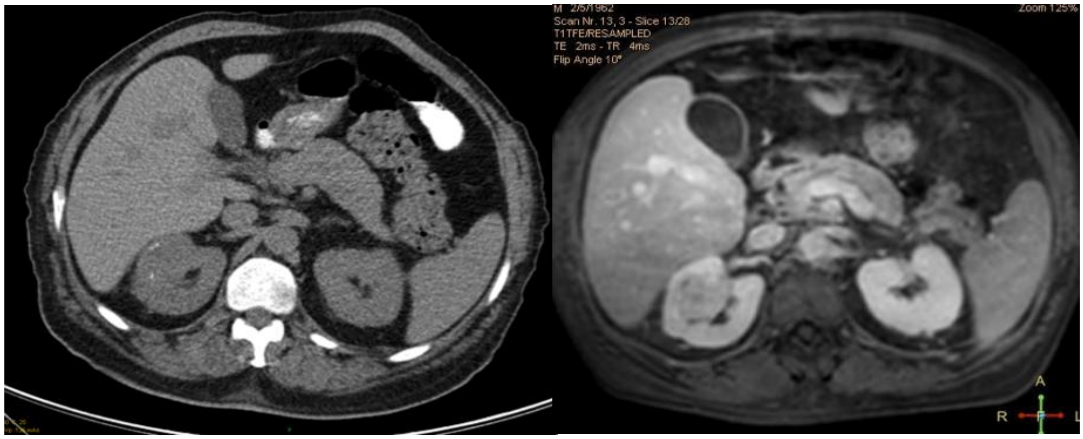

Figure 1. Right kidney tumour. A) Abdominal CT (without contrast) showing small foci of calcifications; B) T1 GAD-enhanced MRI showing renal sinus invasion.

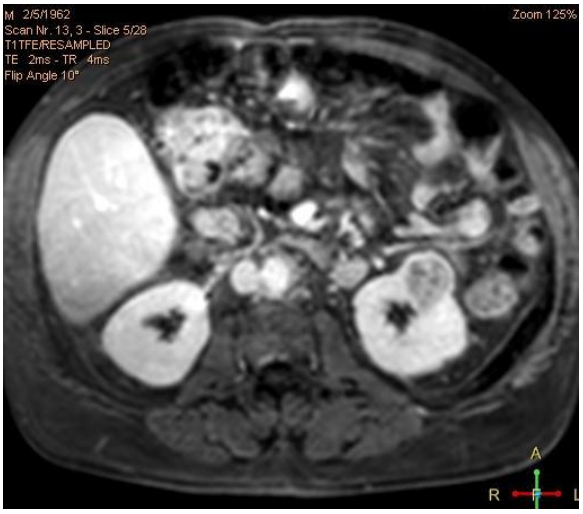

Figure 2. Left kidney tumour. T1 GAD-enhanced MRI displaying a small capsulated lesion without renal sinus invasion.

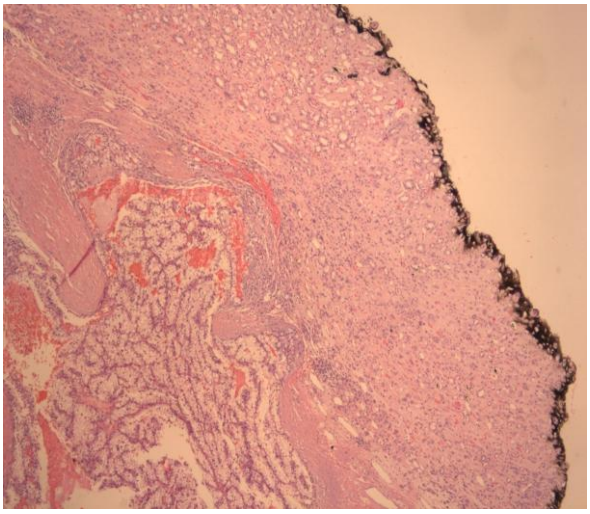

Figure 3. Left kidney tumourectomy histopathology. *Haematoxylin & Eosin (H&E), 40x* – clear cell renal cell carcinoma (CCRCC) showing free margin.

hyperintense signal maintained after gadolinium injection. Invasion of the right renal sinus was also confirmed. The exam showed no intra-abdominal invasion or metastasis, and there was no extension to the renal veins or the inferior vena cava. We achieved a definitive diagnosis after US-guided biopsy of the right kidney revealed clear cell RCC. Preoperative staging required thoracic CT, which was negative for metastasis. Echocardiogram showed dilated left chambers, diffuse hypokinesis of the left ventricle (LV) and depressed LV systolic function (with a 39% ejection fraction), normal right chambers dimensions, no valvular regurgitations and non-dilated inferior vena cava. Pericardium was normal. No images of intracardiac thrombi or tumours were found. Respiratory functional studies confirmed respiratory failure, but a correct evaluation was objected by concurrent acute tracheobronchitis. At that point the pneumology consultant did not consider bronchoscopy to be a fundamental exam for an immediate assessment of the patient. As we had no access to genetic testing, we could not check for VHL gene. After achieving glycaemic control, resolving the respiratory tract infection and completing a four-week period of preoperative respiratory kinesiotherapy, the patient underwent right nephrectomy due to renal sinus invasion but was still suitable for contralateral nephron-sparing surgery – left kidney tumourectomy. The operation went well and no red blood cell transfusion was necessary. The left lesion measured 3.5x3.5x3cm and weighed 14g. Its cut surface showed a yellow mass with haemorrhagic areas, sharply demarcated from the surrounding tissue by a pseudocapsule, and with a 2-mm free surgical margin. Right kidney showed similar macroscopic tumoral aspects. Microscopically the two were CCRCC, Fuhrman grade 2 (Figures 3, 4A and 4B), stage pT1a. There was no multifocality. Two months after the operation, his BP was controlled with once daily perindopril 4mg and long-acting nifedipine 30mg, and his T2DM was being treated

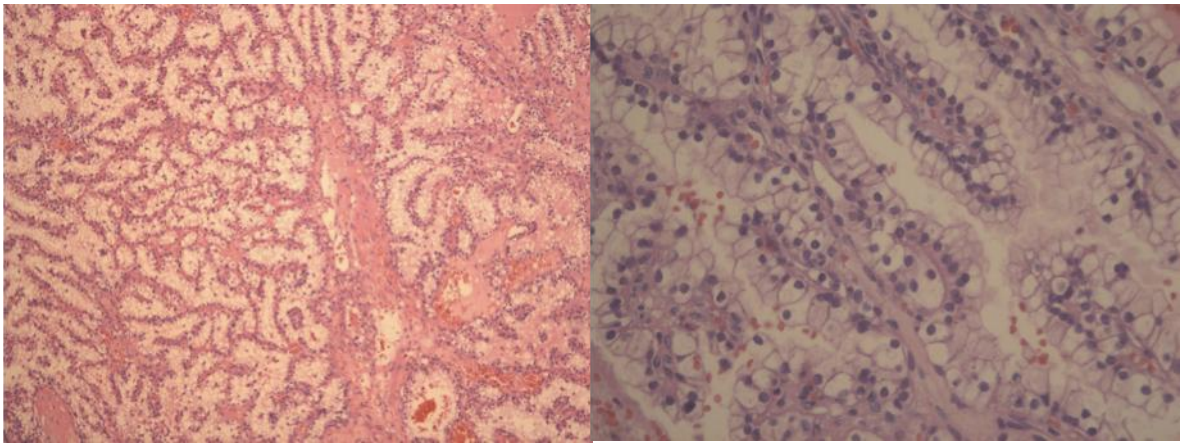

Figure 4. Right nephrectomy histopathology. A) *H&E, 100x* – CCRCC; B) *H&E, 400x* – CCRCC, Fuhrman grade 2.

with diet, slow-release gliclazide 60mg once daily and metformin 1000mg three times a day. He quit smoking, lost 12kg and his BMI went down to 28.7kg/m^2. Blood work revealed marked improvement in HbA1c (down to 6.2%) and renal function remained acceptable (creatinine 1.3mg/dl with an estimated GFR of 78ml/min). His arterial blood gas showed hypoxaemia and normocapnia (PaO_2 68.4mmHg and $PaCO_2$ 45.2mmHg) with a normal pH value of 7.410; bicarbonate and lactate were both in the normal range (respectively 27.7 and 1.0mmol/L). Pulmonary function tests displayed limitation in both small and large airways permeability without significant response to bronchodilating therapy and a reduction in alveolar-capillary CO diffusion, thus confirming partial respiratory failure. The patient was asymptomatic so we stopped BiPAP and after one month started nightly low-dose nasal oxygen therapy (1.5L/min). We also performed whole-body bone scintiscan and head CT, both negative for metastatic lesions. As an outpatient his evolution is being monitored by Internal Medicine, Endocrinology, Urology, Nephrology, and Respiratory Medicine units. Two years after surgery the patient is clinically well, hepatomegaly is no longer detectable, and liver function tests are normal. His GFR is now 84ml/min. Renal and abdominal US reveal no signs of recurrent disease in the treated left kidney or the right renal fossa, and no regional and liver metastasis. Chest CT is negative for lung metastasis. Unfortunately and against our repeated advice the patient does not pursue appropriate antidiabetic diet, making it impossible to maintain glycaemic control (his HbA1c is now 9.1%) despite being treated with sitagliptin 50mg twice a day, metformin 1000mg three times a day and gliclazide 60mg twice a day, and developing mixed dyslipidaemia in spite of treatment with once daily rosuvastatin 10mg and fenofibrate 200mg. His BP is now under control with once daily perindopril 8mg and long-acting nifedipine 60mg.

DISCUSSION

The classic symptom triad of RCC comprising haematuria, abdominal or flank pain and a palpable mass on physical examination frequently means advanced and often metastatic cancer, requiring radical nephrectomy but entailing a poor prognosis. With the revolution of imaging methods for evaluating nonspecific abdominal complaints, more than 70% of RCC cases identified today are “screen-detected” as incidental findings in the evaluation of those symptoms, and as such many kidney tumours now diagnosed are smaller, organ-confined, and frequently appropriate for nephron-sparing approaches with the anticipation of a favourable outcome (Chen D 2011). The prognosis of RCC is related to tumour stage. CT and MRI are both relatively accurate in staging and are the gold standard preoperative assessment tools. Contrast-enhanced CT is the imaging modality of choice for evaluating patients with a renal mass and it is generally precise in the diagnosis and staging of RCC (Israel G 2003). Although not all enhancing renal masses on CT represent RCC, any solid renal mass should be considered as such until proven otherwise. Some of the CT aspects in favour of RCC are significant contrast-enhancement (>20UH), central calcification, margin irregularity and heterogeneity. Differential diagnosis includes lymphoma, angiomyolipoma, pseudotumours and metastatic disease to the kidney. Development of multidetector CT allowed dynamic multiphase image acquisition, enabling multiplanar reformations and three-dimensional volume rendering, thus providing the urologic surgeon with important preoperative information (Chen D 2011). Multiphase MRI with pre- and post-gadolinium phases may be required for certain patients with renal failure, in order to prevent contrast nephropathy, or occasionally in cases of equivocal CT scan data on renal sinus infiltration or vena cava invasion. Recently though, there were a few reported cases of gadolinium nephrotoxicity and acute renal failure

in patients with preexisting chronic kidney disease (Ledneva E 2009). Anyway, generically speaking, MRI could be used more safely than contrast CT in patients who have undergone nephron-sparing surgery and who are in need of serial follow-up examinations (Israel G 2003). Percutaneous needle-guided aspiration biopsy is increasingly used for diagnosis of RCC (Israel G 2003). Results are highly accurate (98% sensitivity), with an acceptable low risk and having great impact on the clinical management of these patients (Grimaldi G 1998). Pathologic features to evaluate RCC include TNM stage, Fuhrman grade, histological subtypes and multifocality. Chest CT, brain CT, and bone scan are necessary when the patient has localising clinical symptoms, for large renal lesions (>7cm), or if there is evidence suggesting higher clinical stage, such as adenopathy or adjacent organ / renal vein involvement (Motzer R 2009). In our patient we decided to perform these exams due to the existence of synchronous bilateral tumours, one of which invaded the renal sinus, to look for possible metastases which were not found. According to a review by Klatte T (2007) there is no statistically significant difference between non-metastatic synchronous bilateral or unilateral RCC for cancer-specific survival. Partial (nephron-sparing surgery) or radical surgical excision is the only effective treatment for clinically localised RCC. Synchronous bilateral tumours should be treated as separate primary lesions, and both surgically resected. Bilateral RCC is a challenge to the urologist, because preserving renal function is critical. In cases of bilateral disease, the presence of a small tumour (<4cm) in one kidney allows safe partial nephrectomy without compromising cancer-free survival (Morgan W 1990). Partial nephrectomy, however, is technically challenging and requires good surgical expertise. Recent surgical options, such as minimally invasive surgery and laparoscopic partial or radical nephrectomy are accompanied by more frequent complications than the classic methods. Image-guided ablation using radio frequency or cryoablation equipment, increasingly applied to treat small renal masses in younger and healthier patients, appears to have a significantly higher risk for local recurrence of RCC comparing to partial nephrectomy, and is not currently recommended (Campbell S 2009). Facing a patient with synchronous bilateral solid renal masses, the surgical plan aims to accomplish two goals: complete resection of the tumour and maintenance of renal function to keep the patient off definitive haemodialysis, which bilateral nephrectomy otherwise implies and can only be prevented by nephron-sparing surgery. Whenever possible, it is also better to perform surgery on both kidneys in the same operative time. It is pivotal to know the basal (preoperative) GFR, as previous chronic kidney disease may progress more quickly to renal failure after surgery (Grimaldi G 1998) and appropriate prophylactic measures can be taken. It is also important to consider the patient's comorbidities, because complications from coexistent pathologies can deteriorate the clinical situation during and after surgery. In our case the respiratory status was found to contraindicate pneumoperitoneum and laparoscopic approach. Although the discovery of very small RCC will not ensure reduction in cancer related mortality, recent reports have demonstrated that in tumours under 4cm partial nephrectomy can be performed safely without compromising cancer-free survival (Lerner S 1996). In the year 2000 a report from Mayo Clinic showed a 10% long-term haemodialysis rate after bilateral surgery for sporadic synchronous RCC (Blute M 2000), but in other series no patients required dialysis (Chen DY 2011). In the last series, with a mean follow up of 52 months, there was a 5-year overall survival of 84.5% and a disease specific survival of 93.3% for bilateral non-familial RCC patients. Our patient's anorexia lasted only one week (improving after the introduction of antidepressant therapy) and surfaced in reaction to one brother's suicide, thus seemingly unrelated to the patient's malignancy. Also Stauffer's syndrome, a paraneoplastic constellation of signs and symptoms of liver dysfunction not caused by tumor infiltration of the organ itself but arising instead due to the presence of renal cell carcinoma, was not considered in this case because liver function tests in Stauffer's syndrome usually reflect cholestasis with or without jaundice, and our patient's abnormalities were cytolytic and a mere result of the acute infectious process, as proven by the test results having returned to normal after antibiotic treatment.

CONCLUSION

Kidney cancers are repeatedly being diagnosed fortuitously in asymptomatic patients undergoing workup for other reasons. These findings often happen when tumours are small and before they exhibit symptoms, which means we would otherwise uncover them later rather than sooner. After histopathologic confirmation of the diagnosis through a guided percutaneous kidney biopsy, the best treatment method should save the most renal tissue, aiming to avoid permanent haemodialysis. Nevertheless, nephron-sparing surgery is only a realistic option for lesions found at an early stage, because renal neoplasms are frequently advanced before they become symptomatic. Primary renal cancer represents 2-3% of all malignant tumours. RCC is the most frequent form of kidney neoplasm but synchronous bilateral non-familial RCC is seldom seen, particularly in people under the age of 60. Our patient was a 49-year-old man with several comorbidities (T2DM, obesity, heavy smoking, high alcohol intake), admitted for respiratory failure but whose study ended up revealing bilateral RCC lesions, still eligible for nephron-sparing surgery in one kidney and thus preventing the need for dialysis. Postoperative surveillance of partial nephrectomy implies routine imaging

of the remaining renal unit throughout the patient's life. Looking out for distant metastasis is mandatory for a long period after surgery, because secondary lesions may occur late in time, and the control of all pathologic factors that could lead to renal function deterioration is of the utmost importance.

REFERENCES

Blute ML, Amling CL, Bryant SC, Zincke H (2000). Management and extended outcome of patients with synchronous bilateral solid renal neoplasm in the absence of von Hippel-Lindau disease. Mayo. Clin. Proc. (75). Pp.1020-6

Campbell SC, Novick AC, Belldegrun A, Blute ML, Chow GK, Derweesh IH (2009). Guidelines for management of the clinical T1 renal mass. J Urol. (182). Pp. 1271-9

Chen DY, Uzzo RG (2011). Evaluation and management of the renal mass. Med. Clin. N. Am. 95. (1). Pp.179-89

Cohen HT, McGovern FJ (2005). Renal cell carcinoma. N. Engl. J. Med. (353). Pp.2477-90

Eble JN, Togashi K, Pisani P (2004). WHO histological classification of tumours of the kidney. Pp.9-87.

Grimaldi G, Reuter V, Russo P (1998). Bilateral non-familial renal cell carcinoma. Ann. Surg. Oncol. (5). Pp.548-52.

Israel GM, Bosniak MA. (2003). Renal imaging for diagnosis and staging of renal cell carcinoma. Urol. Clin.

N. Am. (30). Pp. 499-514

Klatte T, Wunderlich H, Patard JJ, Kleid MD, Lam JS,

Junker K, Schubert J, Böhm M, Allhoff EP, Kabbinavar FF, Crepel M, Cindolo L, De La Taille A, Tostain J,

Mejean A, Soulie M, Bellec L, Bernhard JC, Ferriere JM, Pfister C, Albouy B, Colombel M, Zisman A, Belldegrun AS, Pantuck AJ (2007). Clinicopathological features and prognosis of synchronous bilateral renal cell carcinoma: an international multicenter experience. BJU Int. (100). Pp.21-5.

Ledneva E, Karie S, Launay VV, Janus N, Deray G (2009). Renal safety of gadolinium-based contrast media in patients with chronic renal insufficiency. Radiol. (250). Pp.618-28

Lerner SE, Hawking CA, Blute ML, Grabner A, Wollan PC, Eickholt JT, et al (1996). Disease outcome in patients with low-stage renal cell carcinoma treated with nephron-sparing or radical surgery. J. Urol. (155). Pp.1868-73

Morgan WR, Zincke H (1990). Progression and survival after renal-conserving surgery for renal cell carcinoma experience in 104 patients and extended follow-up. J. Urol. (144). Pp. 852-7

Motzer RJ, Agarwal N, Beard C, Bolger GB, Boston B, Carducci MA, Choueiri TK, Figlin RA, Fishman M, Hancock SL, Hudes GR, Jonasch E, Kessinger A, Kuzel TM, Lange PH, Levine EG, Margolin KA, Michaelson MD, Olencki T, Pili R, Redman BG, Robertson CN, Schwartz LH, Sheinfeld J, Wang J (2009). NCCN clinical practice guidelines in oncology: kidney cancer. J. Natl. Compr. Canc. Netw. (7). Pp.618-30.

Rashid S, Shafiq M, Arshad M, Zafaar MR (2008). Bilateral multifocal renal cell carcinoma. Prof. Med. J. (15). Pp.400-2.