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Case Report

Gross hematuria: Renal cell carcinoma mimicking a renal arteriovenous malformation ☆

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ABSTRACT

The differential diagnosis between renal arteriovenous malformations (AVM) and cancer may be a challenge, due to the similar clinical and imaging findings. Herein, we report the case of an 80-year-old male patient presenting gross hematuria, initially diagnosed and treated with embolization for a renal AVM. Due to the recurrence of hematuria and rapid progression and changes of the vascular lesion with detection also of an intralesional solid nodule, a radical nephrectomy was performed revealing the presence of a renal cell carcinoma (RCC). Renal cell carcinoma and renal AVM can be difficult to differentiate from one another, for this reason a short-term follow-up should be carried out in patients diagnosed and treated for renal AVM to confirm the resolution of AVM or to assess any changes, such as atypical neovascularization or intralesional renal masses, which may increase the suspect of a hidden renal tumor.

Introduction

Hematuria is defined as the presence of red blood cells in the urine, and it is classified into macroscopic or gross hematuria, which is clinically visible, or microscopic hematuria, which is visible only on urinalysis or urine microscopy. Hematuria may be determined by several benign and malignant diseases. Causes of hematuria may be of renal, postrenal, hematological, and vascular origin with different incidences depending

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by sex, age, risk factors, and race. In adult population, hematuria is more frequently caused by to nephrolithiasis, benign prostatic hypertrophy, or malignancy [1,2]. Among malignancies, renal cell carcinoma (RCC) is the most frequent cause [3–6]. Patients with RCC commonly present gross hematuria, abdominal pain, weight loss fever, a thin, malnourished appearance, vision abnormalities, and elevated blood pressure, asymmetric enlargement of testicles or varicose veins of the testis in male patients. RCC can be also silent for a long time and discovered incidentally in ER settings in advanced stages and sometimes with vascular invasion [5]. On the other hand, renal arteriovenous malformation (AVM) represents a rare renal condition with an estimated prevalence in general population of 0.04% [6,7]. The signs and symptoms of renal AVM may vary from asymptomatic to hematuria (72%), hypertension (50%), flank pain, abdominal mass, perinephric hematoma, flank bruit, and high-output heart failure [10,11] and radiologic diagnosis may be challenging due to the variable appearance of AVM [8–11]. Both RCC and AVM may be suspected in case of flank pain and micro- or macro-hematuria [7,8] and a correct differential diagnosis between AVM and RCC may be challenging. Herein, we report the case of a patient initially diagnosed with AVM with a final diagnosis of RCC.

Case report

An 80-year-old male patient referred to our emergency department for gross hematuria and left flank pain for the last 7-days. Medical history was positive for dyslipidemia, and benign prostatic hypertrophy treated with atorvastatin and alfuzosin, respectively. The patient denied any previous renal diseases, trauma, or surgery. Physical examination revealed a treatable abdomen and mild edema of the lower limbs. Routine blood tests were within normal ranges except for the presence of anemia (hemoglobin: 10 g/dL, normal value 11.5-17.5 g/dL), and thrombocytopenia (115 10^3/mm^3, normal value 150-400 10^3/mm^3). Urinary test confirmed the presence of gross hematuria. Bladder POCUS ultrasonography was performed. At US, a coarse echogenic area in the bladder referred as a blood clot was detected and cystoclysis was performed. Because of persistent macro-hematuria and acute onset of right leg pain, an abdominal-pelvic CT, and lower limbs angiography were performed.

A CT multiphase protocol was performed (noncontrast, arterial, corticomedullary, parenchymal, and excretory phases) with intravenous contrast (1.0-1.5 mL/kg injected at 3.5 mL/s, followed by 50 mL of a saline bolus injection). During the arterial phase at the mesorenal region of the left kidney, the renal artery appeared in communication with multiple tangled ectasic intraparenchymal venous vessels. Venous thrombosis of the right femoral popliteal axis extending from the deep veins to the external iliac origin was also detected. A CT final diagnosis of left intraparenchymal renal AVM and deep vein thrombosis was formulated (Figs. 1 A and B).

The patient underwent preoperative digital subtraction angiography (DSA), that confirmed the presence of the arteriovenous fistula at the mesorenal site of the left kidney, and the AVM was embolized with controlled-release coils

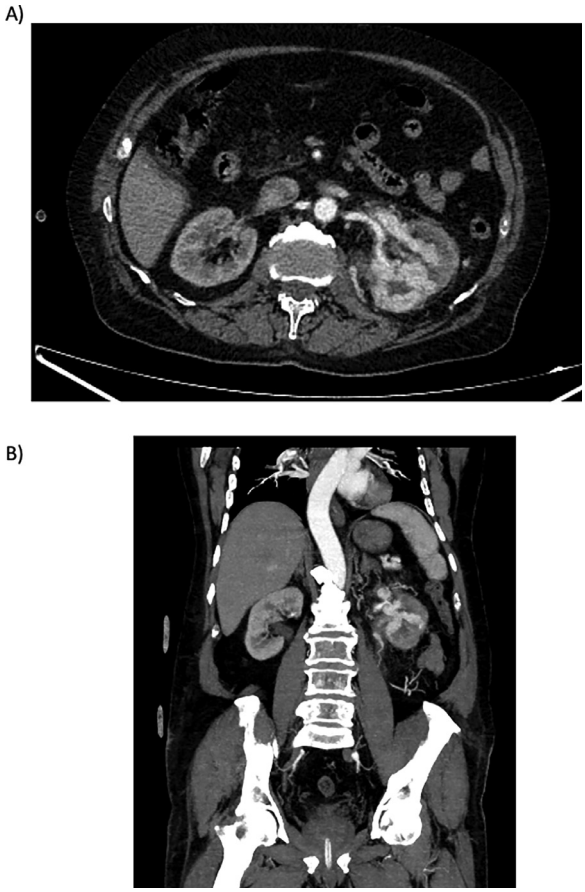

Fig. 1 – Axial CT scan during the arterial phase (A) showing early filling of the venous vessels. due to direct communication with the renal artery. -Coronal MPR CT (B) image showing the vascular tangle at the left mesorenal site.

(Figs. 2 A and B). A few days after the procedure, the patient was discharged in stable general condition with a urinary chemical test negative for micro or macrohematuria.

However, after 5 months, the patient referred to our emergency department due to a relapse of gross-hematuria and severe asthenia. A routine blood test revealed the presence of severe anemia (Hb: 6.9 g/dL) that required blood transfusion. Thus, the patient underwent an abdominal-pelvic CT-angiography. The CT findings were significant different from the previous CT. At the mesorenal site of the left kidney, the vascular lesion was significantly changed in form, appearance and dimension. The AVM was increased in volume, linked to a spiderweb venous reticula with undetectable borders and multiple left renal intraparenchymal fistulas with direct drainage into the renal vein and a dense perirenal reticular venous system were detected. Moreover, a thrombotic filling defect of the left renal vein was visualized (Figs. 3 Aand B). At the mesorenal/polar inferior region strictly adjacent and posterior to the previously reported AVM fistula, a solid exophytic nodule (<50%) was appreciable (Figs. 4 A-D). Due to the extreme anemia and uncontrollably hematuria in emergency rooms, a new embolization procedure was performed

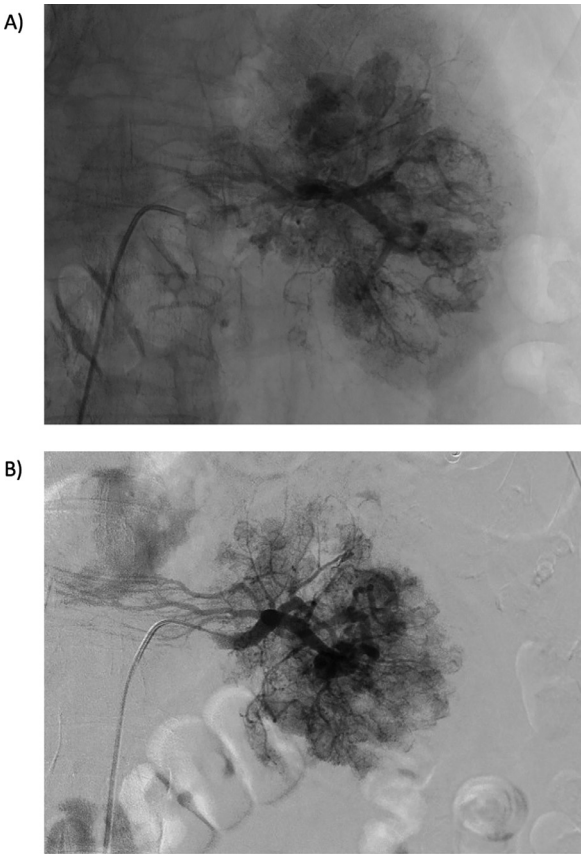

Fig. 2 – (A and B) Angiographic embolization of the left renal AVM showing arterialized flow inside the renal vein and early filling of the left renal vein.

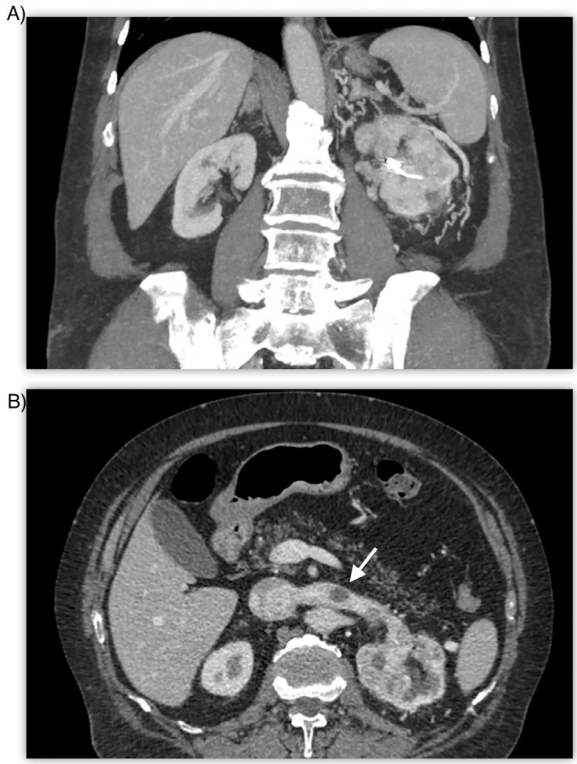

Fig. 3 – Contrast-enhanced Coronal MPR CT during the nephrographic phase showing (A) multiple left renal intraparenchymal fistulas with direct drainage into the renal vein and a dense perirenal reticular venous system. (B) Axial CT (nephografic phase) a thrombus in the renal vein with a maximum dimension of 18mm(arrow) is detected.

with the closure of the majority of fistulous tracts. Radical nephrectomy was carried out because of a suspect diagnosis of renal malignancy supported by CT findings of the changes in morphology and appearance of the vascular lesion and for the detection of a solid intralesional nodule. The histological examination revealed the presence of Fuhrman grade 2 clear cell RCC and a massive and chaotic neo-angiogenesis at the renal cortex. linked to a tumoral The thrombus of the renal vein was determined by neoplastic invasion, meanwhile no AVM was detected at histology.

Discussion

Renal cell carcinoma (RCC) represents the most frequent primary malignancy of the kidney (92%) [3,4]. There are several histological RCC subtypes, among them the most frequent histological subtypes representing more than 90% of RCC are clear renal cell carcinomas (ccRCC), papillary renal cell carcinomas (pRCC), and chromophobe renal cell carcinomas (crRCC). The most common variant is clear renal cell carcinoma (70%-75%), representing in up to 95% of cases a sporadic malignancy (95%), while the remaining 5% are associated with hereditary syndromes (Von Hippel-Lindau disease, tuberous sclerosis) [5,6]. Clear renal cell carcinoma originates from the proximal convoluted tubule epithelium (renal cortex) and due to its characteristic growth pattern, some patients are asymptomatic, and tumors are discovered lately and incidentally during other examinations. Hematuria, abdominal discomfort, and a palpable abdominal mass represent the typical symptoms of RCC [1–3], however only less than 10% of patients present these typical manifestations. Furthermore, several cases of RCC, especially in the early stages, are frequently asymptomatic or with only mild and non-specific symptoms [7]. Indeed, it is not infrequent to reach a diagnosis of RCC performing radiological procedures required for other reasons [7,8]: it has been reported that, probably due to the rapid development and use of cross-sectional imaging studies, more than half of RCC diagnoses are discovered incidentally (incidentaloma). Among available procedures, one of the most effective imaging techniques for locating and characterizing renal masses is represented by the contrast-enhanced CT [7]. Corticomedullary, nephrogenic, and delayed excretory phases are included in most CT protocols for renal mass. The analysis of these phases is useful in classifying renal masses and may suggest the RCC histological subtype. Moreover, CT accurately defines extension and relation of renal mass to hilar structures, these anatomic information support surgeon in preoperative planning.

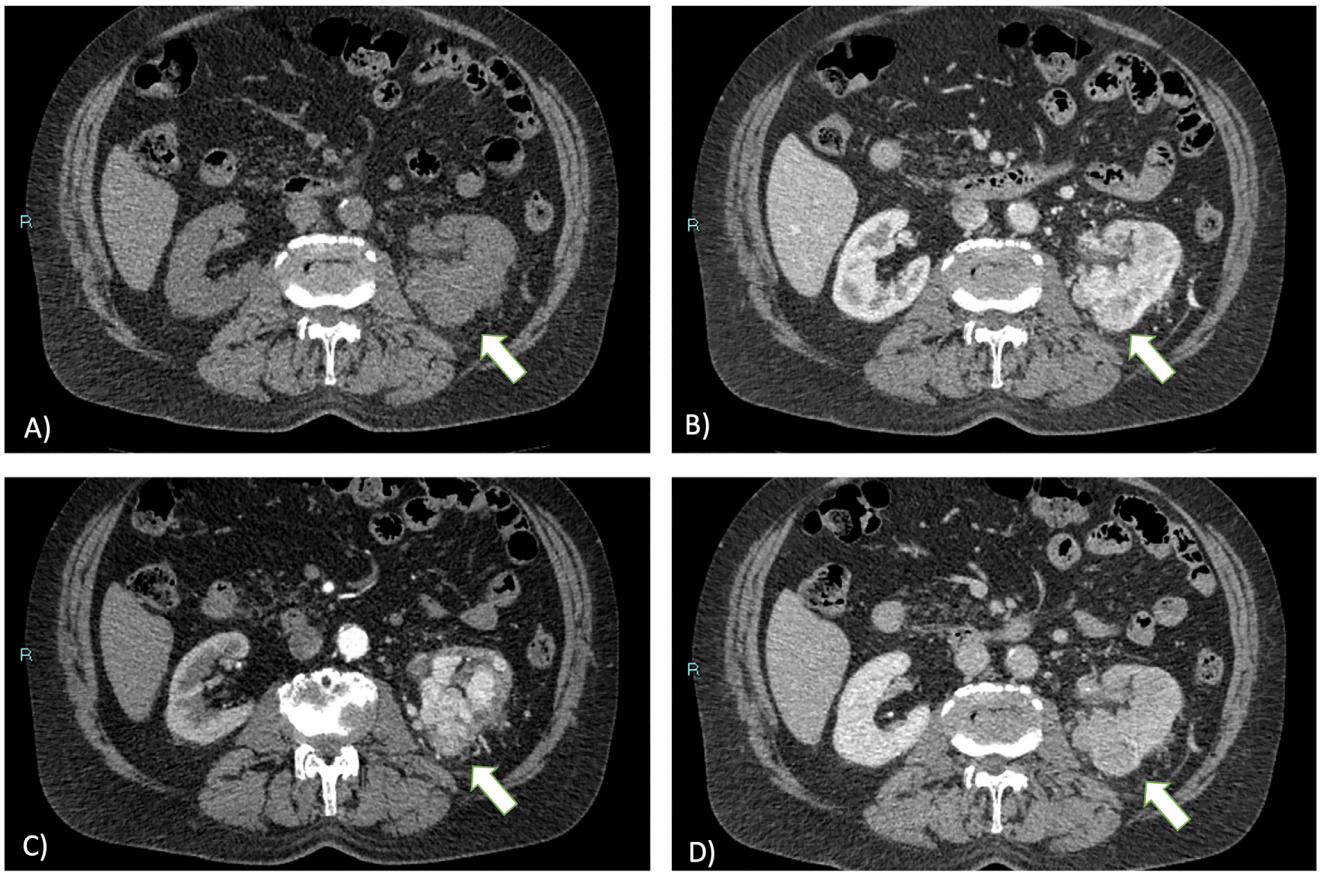

Fig. 4 – CT axial scan showing phase without contrast (A), during the arterial phase (B) and the nephrographic phase (C). The left kidney shows reduction of cortical-medullary differentiation and the presence of nodular partially exophytic lesion at the lower mesorenal/polar site with a maximum size of 17mm (arrows). This lesion presents a peripheric area of contrast enhancement, and shows marked intranodular hypodensity even in the delayed phase (D).

The arterial phase underlines the anarchic angiogenesis also revealing tumor-related arteriovenous fistulas and provides helpful preoperative information on the vascular anatomy and hilar architecture and the distance between the tumor and hilar structures. Three-dimensional volume rendering, multiplanar reformatting, and maximum intensity projection [9] are helpful to accurately define the relationship between the tumor and hilar vascular structures.

The excretory phase emphasizes the relation between the tumor and collecting system, giving important information for the surgical nephron-sparing approach when considered.

Although CT imaging usually clarifies the nature of incidentally discovered renal masses, the diagnosis of RCC can be challenging in some cases reason why RCC is considered the great mimicker at imaging [9]. One of the atypical appearances of RCC is a vascular lesion appearance making the differential diagnosis with AVM and other vascular renal lesion such as hemangiomas, anastomosing hemangiomas, lymphangiomas, solid intravascular papillary endothelial hyperplasia extremely hard [10] However, a prompt correct diagnosis is essential to start as soon as possible the right treatment in each situation, avoiding delay in diagnosis, which may lead to tumor progression or other clinical complications.

On the other hand, AVM is extremely rare [6,7] and it can be congenital or acquired (being reported after trauma, malignancy, or renal biopsy) [7,11], although the term “AVM” more commonly refers to the congenital type of vascular abnormality, whereas acquired malformations are usually referred to as arteriovenous fistulas [12]. AVN is characterized by an aberrant vascular shunt between the arterial and the venous system due to the absence of an intervening capillary bed [8]. The rarity of AVMs makes its confident differential diagnosis with RCC challenging.

RCC is a highly vascular tumor that can develop from VHL gene mutations, which causes aberrant expression of growth factors that promotes angiogenesis, like vascular endothelial growth factor (VEGF). These angiogenic factors are essential for the growth of RCC and may determine the development of tumor related AVMs [8,11]. Furthermore, AVM may be difficult to differentiate from RCC, due to the tumor related thrombosis and/or the neovascularization processes, which may lead to RCC mimicking an AVM [7,8] but there are also

cases of benign AVM mimicking RCC described in the literature [12]. In our case, RCC appeared mostly characterized by an angiogenic vascular/anarchical reticulum and a centimetric solid intralesional lesion was detected only after the first embolization making the diagnosis at the first instance extremely difficult.

The difficulties in the differential diagnosis between AVM and RCC are linked to the possible onset of aberrant blood shunt in RCC, caused by the faulty vasculature of RCC, which results in an up-regulation of VEGF-1 and platelet-derived growth factor (PDGF), leading to growth of the tumor and its vessels [11–14]. On the other hand, renal benign AVM represents a rare disease, affecting less than 1% of the general population, which may present with several different appearance at imaging. The stromal tissue content of AVMs may be variable, affecting the way it appears in cross-sectional imaging: the high flow vascular component might not clearly visible if there is a greater proportion of fibrous stroma. In these cases, associated with the aberrant vasculature and low-pressure vascular component of AVM, the diagnostic sensibility decreases, and renal angiography may help to reach a definitive a diagnosis by highlighting the vasculature abnormalities [9].

Cases of misdiagnosis between AVM and RCC are being increasingly reported in the literature, Vasvada et al. reported 6 cases of RCCs firstly misdiagnosed as AVM [15]. On the other hand, Kossefi et al. reported a case of a woman with an incidental renal vascular mass considered a hypovascularized kidney tumor, which instead resulted to be an AVM associated with left renal vein thrombosis [16].

Similar to our case, Volin et al. [8] reported a patient initially diagnosed and treated for AVM who at 1 year follow up MRI presented a 6 cm metastatic RCC, that was not identified prospectively and retrospectively at previous follow up MRI and CT studies.

We reported a case of a patient with gross hematuria firstly diagnosed and treated for AVM who for the relapse of hematuria underwent CT 5 months later that showed significant changes of the lesion with an intralesional centimetric solid lesion not detected at the first CT examination. Our case remarks how RCCs and AVMs are 2 clinical entities may be extremely difficult to differentiate, and that the RCC diagnosis should be considered in patients with AVMs unresponsive to embolization procedures. On the other hand, because a definitive differential diagnosis between a benign AVM lesion and RCC with tumor related AVM formation cannot be always possible, a short term imaging follow-up (3-6 months) is recommended in patients with AVM treated with embolization.

In conclusion, due to the difficulties in the differential diagnosis process, it is important to understand the relationship between RCC and AVMs for patient safety and surgical planning. A strong index of suspicion is required to identify these potentially concomitant lesions due to their similarity in radiological appearance [13] and a clinical and laboratory follow-up after 3-6 months may be recommended to confirm the resolution of AVM, as well as to evaluate the presence of atypical intralesional neo-vascularization or renal masses, which may increase the suspicion of a hidden renal tumor.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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