Case Studies

A 40-Year-Old African American Woman With Sickle Cell Trait, a Renal Cell Mass, and an Ulcerated Scalp Lesion

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CLINICAL HISTORY

Patient: 40-year-old African American woman.

Chief Complaint: Painless hematuria.

History of Present Illness: The patient had 2 episodes of painless gross hematuria before seeking treatment in our emergency department; she reported no other symptoms. Her urinalysis results were positive for hemoglobin and revealed more than 50 red blood cells per high-powered field on microscopic examination. A 3-phase computed tomography (CT) scan revealed an enhancing 3.9 × 2.5 cm lesion in the superior/interpolar region of the right kidney, which suggested renal cell carcinoma or transitional cell carcinoma. A renal biopsy guided by the CT image was not diagnostic. A nephrectomy was performed.

Family History: The patient’s maternal grandmother had died of breast cancer.

Social History: The patient reports never being a smoker and reports no recreational drug use.

Follow-up: Two months after her nephrectomy, a positron emission tomography (PET) scan performed on the patient did not reveal metastatic disease. Two months later, she developed a painful scalp lesion, which slowly grew over the next several months, eventually ulcerated, and did not heal despite appropriate wound care. A biopsy of the lesion had a histologic appearance similar to that of the nephrectomy specimen.

Keywords: sickle cell trait, hematuria, renal medullary carcinoma

Abbreviations

CT, computed tomography; PET, positron emission tomography; UTI, urinary tract infection; RCC, renal cell carcinoma; RMC, renal medullary carcinoma; AFIP, Armed Forces Institute of Pathology; HIF, hypoxia-inducible factor; TP53, tumor protein 53; VEGF, vascular endothelial growth factor

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Shortly after undergoing skin biopsy, the patient developed new-onset abdominal pain and sought treatment in the emergency department. A computed tomography (CT) scan of her abdomen and pelvis revealed a 1.1 cm pulmonary nodule with mass effect, in a lung base that was suggestive of metastatic disease. A 1.8-cm soft-tissue mass arose at the resection site with a differential diagnosis of recurrent disease or scarring. A positron emission tomography (PET)-CT scan was subsequently performed, which revealed recurrent disease in the right renal fossa and diffuse abdominal and pulmonary metastatic disease. The patient underwent a follow-up skin biopsy.

Questions:

1. What are this patient’s most striking clinical, laboratory, and radiologic findings?
2. This set of clinical, laboratory, and radiologic findings suggests what conditions?
3. What should be the next step in performing a work-up of the kidney mass?
4. What does the resection specimen show?
5. What is this patient’s most likely diagnosis?
6. What does the follow-up skin biopsy show?
7. What is the significance of the results of the follow-up skin biopsy?
8. What is the prognosis of the patient’s disease?

Possible Answers

1. The patient’s most striking clinical finding was painless gross hematuria. Gross hematuria was
reported in her medical history but was not identified on the initial urinalysis findings (the urine specimen color was yellow); however, her urinalysis results revealed an elevated hemoglobin level via dipstick testing, which was confirmed by microscopic examination of the urine. The patient reported no other urinary or systemic symptoms, such as dysuria, fever, chills, night sweats, or weight loss. On urinalysis, the leukocyte esterase and nitrite results were negative, the urine white blood cell count was not increased, and the urine protein level was within normal limits. The blood urea nitrogen and creatinine levels were also within normal limits (Table 1). The imaging studies identified a mass in the superior pole of the right kidney.

2. Common etiologies for hematuria include urinary tract infection (UTI), calculi, glomerular disease, menstrual-bleeding contamination, and malignant neoplasms. In a prospective analysis of 1930 patients with hematuria, it was revealed that 13% had UTIs, 12% had bladder tumors, 10% had nephrologic diseases, 2% had kidney stones, 0.6% had kidney tumors, and 0.1% had upper tract urothelial carcinoma. Of note, for 61% of patients, no cause was identified for hematuria. An occult UTI may be asymptomatic; however, dysuria and fever are commonly observed in conjunction with hematuria. One would also expect to observe the presence of pyuria and hematuria, as well as positive leukocyte esterase and nitrite test results. Renal calculi commonly present with gross hematuria; patients with these conditions typically experience unilateral flank pain. In glomerular disease, azotemia would be expected, along with some degree of proteinuria, dysmorphic red blood cells, and red cell casts on urine microscopic examination. Menstrual contamination is a common cause of false hematuria; hematuria is rarely associated with urinary tract endometriosis.

Gross hematuria, one of the 6 sickle-cell nephropathic manifestations described by Berman in 1974, is often associated with sickle cell trait. The other sickle cell nephropathic manifestations described in the literature include papillary necrosis, nephrotic syndrome, renal infarction, inability to produce concentrated urine, and pyelonephritis. Davis et al describe renal medullary carcinoma as the seventh known sickle cell nephropathic manifestation. Hematuria is usually benign and most likely occurs due to bleeding beneath the renal pelvic epithelium. Occult malignant neoplasms are also a common cause of painless hematuria. The primary tumor can grow anywhere along the urinary tract, including the bladder, ureter, or kidney. The most common malignant neoplasm observed with hematuria is bladder cancer. It is uncommon that hematuria is associated with an upper urinary tract malignant neoplasm. Our patient has a mass in her right kidney that was potentially responsible for her gross hematuria.

3. To further evaluate the mass in the patient's right kidney, a histologic diagnosis is necessary. In a series of 2675 renal masses, 88% were proven to be malignant and 12% to be benign; as the size of the mass increased, so did the risk of malignancy. Smaller tumors were less likely to be malignant than larger tumors; however, of tumors less than 1 cm in diameter, 62% were malignant. Our patient's tumor was 3.9 cm in diameter, as determined by CT scan; it had an 87% risk of being malignant. Due to the high risk of malignancy, a histologic diagnosis was sought.

Clear cell renal cell carcinoma (RCC) is the most common malignant renal tumor (71%), followed by papillary RCC (14%), chromophobe RCC

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HPF, high power field; NA, not applicable.
The most common types of benign tumors include oncocytoma (74%), angiomyolipoma (11%), metanephric adenoma (3%), and others (12%).

To rule out malignancy, a CT scan–guided core biopsy was attempted; however, the results did not yield a diagnosis. A right nephrectomy was subsequently performed for definitive histologic diagnosis, based on the presumptive risk of malignancy.

The right kidney resection specimen revealed a well-circumscribed, firm, yellowish-tan mass, with areas of hemorrhage, present in the upper lobe, measuring 3.7 × 3.5 × 2.0 cm.

Adherence of the renal capsule firmly adheres to this location to the upper lobe of the kidney.

On microscopic inspection, the tumor had a predominantly tubulopapillary growth pattern; certain areas had a reticular yolk sac pattern within a desmoplastic stroma (Image 3 and Image 4). The tumor subtly permeated the surrounding renal parenchyma. In the renal collecting ducts, tubules with dysplastic epithelium were observed. Nuclei lining the tubules were extremely pleomorphic, with vesicular to coarse chromatin, prominent nucleoli, and mitotic figures (Image 5). Sickled erythrocytes were identified within the dilated tubules (Image 6). Microscopic invasion of the renal capsule was identified at the
point where the capsule adhered to the underlying kidney. There was lymphocytic infiltrate in the renal parenchyma around the tumor.

5. The gross and histologic picture is consistent with a high-grade malignant neoplasm. The picture was consistent with the most common histologic types of RCC, including clear-cell, papillary, and chromophobe.

Clear cell RCC has a golden yellow gross appearance and frequently includes areas of cystic degeneration, necrosis, and hemorrhage. Histologically, it includes cells with clear cytoplasm. Higher grade (ie, Fuhrman grade 4) clear cell RCC can include pleomorphic cells with prominent nucleoli. Papillary RCC is usually manifested as a well-circumscribed light grey to reddish-brown to golden yellow mass. Histologically, it has a papillary configuration, with varying amounts of lipid-laden macrophages within the stroma. Chromophobe RCC is well-circumscribed, with a tan- to brown-colored appearance. On histologic examination, this entity can have a granular oncocytic appearance or be composed of abundant vesicular cytoplasm with plant-like cell walls.6

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Image 3
Predominantly tubulopapillary growth pattern of tumor (H&E staining; magnification, ×100).

Image 4
Reticular yolk sac pattern of tumor within a desmoplastic stroma (H&E staining; magnification, ×200).

Image 5
The nuclei lining the tubules, which are extremely pleomorphic, with vesicular to coarse chromatin, prominent nucleoli, and mitotic figures (H&E staining; magnification, ×200).

Image 6
Sickled erythrocytes identified within the dilated tubules (H&E staining; magnification, ×400).
The histologic picture in this case is most consistent with collecting duct RCC or renal medullary carcinoma (RMC). These entities commonly have a tubulopapillary growth pattern, including high-grade pleomorphic cells with prominent nucleoli. Immunohistochemistry cannot differentiate between these 2 entities, to our knowledge; hence, additional history and histologic clues must be considered. First, the patient has a history of sickle cell trait. Second, sickled erythrocytes are present within the high-grade tumor. This combination of factors is most consistent with RMC. This diagnosis was confirmed by an expert consultant.

RMC was first described in 1995 by Davis et al of the Armed Forces Institute of Pathology (AFIP) as the seventh sickle cell nephropathy. RMC is observed most often in young African American males with sickle cell trait. It has also been described in sickle cell disease and hemoglobin SC disease. The male to female ratio for this disease is 1.9:1; however, in patients younger than 9 years of age, this ratio is 5:1. The mean age at diagnosis is 19 years (range, 5-40 years). One case has been reported of a 69-year-old Abrobrazilian woman with sickle cell trait who also had conventional renal cell carcinoma. Common symptoms of RMC include hematuria, flank pain, and weight loss.

RMC has the characteristic histologic pattern of reticular growth similar to yolk sac testicular tumors of reticular type. Additional patterns have been described, including tubular, solid, adenoid cystic, sarcomatoid, and microcystic with micropapillations. Also characteristic of this disease is prominent stromal desmoplasia, which can be collagenous, edematous, mucoid, or myxoid. Sickled erythrocytes are usually identified in the tissues; invasion of the renal parenchyma is almost universally present. The appearance of these tumor cells is high-grade and characterized by dark eosinophilic cytoplasm with large pleomorphic nuclei and prominent nucleoli. Rhabdoid-like cells have also been identified in these tumors. Given the characteristic morphologic characteristics of the specimen and the patient’s history of a sickling disorder, the diagnosis of RMC can be made without ancillary tests in this case.

RMC is thought to be derived from the epithelium of the collecting ducts near the renal papillae. The acidic, hypertonic, and hypoxic microenvironment of the renal medulla promotes sickling of susceptible erythrocytes. Further, it has been proposed that hypoxia-inducible factor (HIF, OMIM#603348), a transcription factor that regulates gene expression in hypoxia, is induced in the renal medulla microenvironment. HIF induces tumor protein 53 (TP53, OMIM#191170) expression, which leads to apoptosis. In tumors lacking p53, the expression HIF induces the angiogenic factor vascular endothelial growth factor (VEGF, OMIM #192240). VEGF subsequently upregulates BCL-2 (OMIM #151430), which inhibits apoptosis. One proposed molecular mechanism for RMC pathogenesis relies on the expressions of VEGF, HIF, and TP53.

Immunohistochemical profiling of RMC has shown that it expresses cytokeratin pool (AE1/AE3), low-molecular-weight cytokeratins (CAM 5.2, 35BetaH11), and epithelial membrane antigen. Coexpression of vimentin is also common. High molecular weight cytokeratins, which are usually undetectable or only weakly positive, have shown that RMC loses the expression of INI1, as demonstrated by immunohistochemical staining. Loss of INI1 is not associated with high-grade renal cell carcinomas or urothelial carcinomas of the renal pelvis, including those with rhabdoid features. No studies have been published, to our knowledge, that directly compare immunohistochemical profiles of collecting duct RCC and RMC. The results of immunohistochemical studies published have not identified a pattern that can differentiate between collecting duct RCC and RMC.

6. The skin biopsy results were morphologically similar to that of the renal cells; the results were consistent with metastatic RMC (Image 7). RMC is an aggressive tumor; it is metastatic in 95% of patients at the time of diagnosis. Our case is unique because the patient had no evidence of metastatic disease at the time of diagnosis or on initial follow-up; however, she developed widespread metastatic disease within months after her initially negative PET result, which attests to the aggressive nature of the disease. RMC is prone to metastasize to the lymph nodes, lungs, and liver. Although RMC commonly metastasizes to the adrenal glands, bone, vertebrae, vagina, ovaries, and orbit, this is the first case study, to our knowledge, of RMC metastasizing to the skin.

7. Survival after diagnosis in one study was 15 weeks, but more recent data shows a mean survival of 19 weeks (range, 2-60 weeks). Four cases have been reported of long-term disease free survival (1 case for 2 years; 2 cases for 2 years, 9 months; and 1 case for 8 years). This patient survived 3 years 1 month from the time of initial diagnosis, making this one of the
few cases of relatively long-term survival. Patients who have survived this disease for prolonged periods of time had localized involvement at the time of diagnosis and were treated with radical nephrectomy.\(^7\)\(^{10}\)\(^{19}\) Also, Simpson et al reported a case in which a patient had no evidence of metastasis after treatment and later developed widespread metastatic disease. This suggests the possibility of a cohort of patients with localized disease that can be successfully treated with surgical intervention; however, as our case demonstrates, close follow-up is necessary because widespread metastatic disease can develop even after the patient is clinically and radiologically free of the disease. LM

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References