Medullary Renal Cell Carcinoma: A Case Study

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Abstract

Medullary renal cell carcinomas are exceedingly rare and essentially uniformly and rapidly fatal. Expeditious diagnosis is crucial. Immediate treatment with a clinical trial or platinum-based chemotherapy is needed for metastatic disease given the aggressive nature of medullary renal cell carcinomas. In this article, we discuss a 24-year-old man with no known significant past medical history who presented with a progressive cough and shortness of breath. After evaluation at an urgent care and four evaluations in the emergency department, the patient was admitted and ultimately diagnosed with metastatic medullary renal cell carcinoma. This case highlights the characteristics, presentation, rarity, and aggressiveness of medullary renal cell carcinoma.

CASE STUDY

The patient is a 24-year-old male with no known significant past medical history who presented to the emergency room (ER) of a community hospital with complaints of worsening cough for the past 1 to 1.5 weeks. His symptoms did not improve with an inhaler and azithromycin that he received from a previous urgent care visit. In the ER, he reported a minimally productive cough and very mild dyspnea on exertion. The viral polymerase chain reaction (PCR) test was negative. A chest x-ray (CXR) showed bilateral lung opacities compatible with pneumonia. The patient was started on doxycycline for presumed atypical pneumonia.

Two weeks later, the patient returned to the same ER with progressive cough and overall malaise. Repeat CXR showed mild improvement in perihilar and reticular predominant opacities bilaterally suggesting mildly improving multifocal pneumonia. The patient was instructed to complete his remaining 3 days of doxycycline, prescribed tessalon perles for supportive care, and discharged home from the ER.

Another 2 weeks later, the patient again returned to the ER and was subsequently admitted with progressive cough and shortness of breath. A CXR revealed worsening diffuse alveolar and interstitial markings bilaterally that may be related to multifocal pneumonia. He underwent his first chest CT with contrast showing multifocal pneumonia, and likely reactive

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mediastinal/bilateral hilar adenopathy that may be related to viral or fungal pneumonia or even sarcoidosis. Imaging also noted a questionable hypoenhancing area in the medial aspect of the right kidney and possible pyelonephritis. The Pulmonology team was consulted, and the patient was started on levofloxacin. Hypersensitivity pneumonitis workup and procalcitonin level were negative, ruling out inflammatory lung disease and infection from a bacterial source. The patient was discharged home 2 days later on levofloxacin with plans for an outpatient bronchoscopy.

Unfortunately, he returned to the ER yet again 5 days after discharge with continued progression of his cough and shortness of breath. He now required supplemental oxygen at 3 liters to maintain adequate oxygenation. Repeat CT chest showed significant progression of multifocal coarse infiltrates and increasing nodular opacities with areas of focal consolidation throughout both upper and lower lobes, along with bulky mediastinal, bihilar, infrahilar, and subcarinal adenopathy and progression of the masslike process within the right infrahilar region (Figure 1). The patient was immediately transferred to another community hospital in order to undergo a bronchoscopy. He quickly developed worsening hypoxia, requiring 6 liters to maintain adequate oxygenation. Two days later, he underwent bronchoscopy, which revealed extrinsic compression in the right mainstem bronchus, bronchus intermedius, and the left mainstem bronchus secondary to the mass noted on the chest CT. A consult to the Oncology team was subsequently requested.

At this point, he continued to require 6 liters of oxygen. He remained afebrile, had persistent tachycardia with heart rates ranging from 100 to 115 beats per minute, and stable blood pressure around 149/95 mm Hg. The physical exam was grossly unremarkable. He continued to deny pain. His medical history was addressed, as well as his parents'. He denied personal medical history but noted a history of colon cancer in his maternal grandmother. His mother noted that she has a history of sickle cell trait.

Differential Diagnosis

Several differential diagnoses for the patient were considered. All infectious etiologies were ruled out following cultures from the

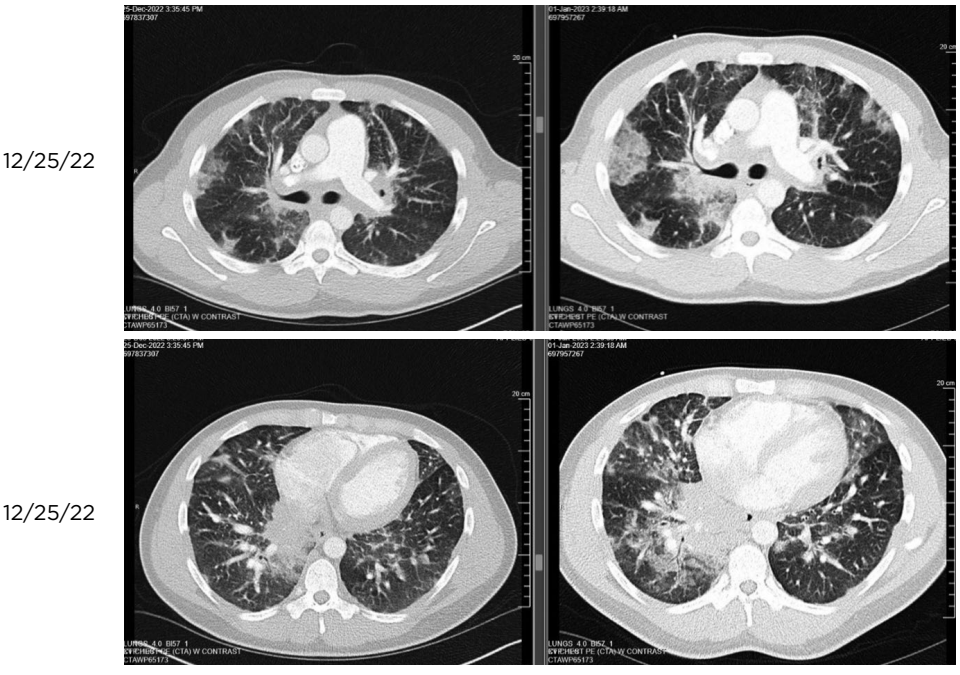

Figure 1. Progression of the patient's malignancy in chest from 12/25/22 (left) to 1/1/23 (right).

bronchoscopy, bronchoalveolar lavage (BAL) gram stain, sputum, blood cultures, and multiple respiratory viral PCR tests. Lymphoma was considered given the aggressive nature and young age of the patient. However, the patient had no B symptoms, and his lactate dehydrogenase (LDH) test was normal, decreasing the possibility of lymphoma. A germ cell tumor such as testicular was another potential possibility. However, LDH, alpha-fetoprotein (AFP), and human chorionic gonadotropin (HCG) blood tests were indicating a low likelihood of a germ cell tumor.

A CT abdomen/pelvis with contrast was obtained and revealed a 5.3 × 5.2 × 3.6 cm lobular low-density masslike process in the medial mid pole of the right kidney, which was indeterminate for solid vs. complex cystic mass but concerning for a neoplastic process. Also noted, although nonspecific, was possible adenopathy with a lobular low-density soft tissue process within the right renal hilus posterior to the right renal artery measuring up to 3.6 × 3.2 × 1.5 cm (Figure 2). With these findings, the differential diagnosis now included urothelial carcinoma or possible renal cell carcinoma.

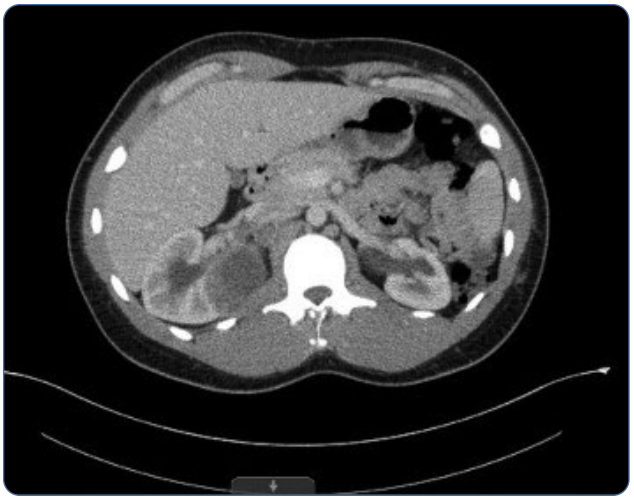

Figure 2. CT abdomen/pelvis demonstrating right renal mass and adenopathy.

Pathology

A thoracic lymph node biopsy was obtained. The final pathology revealed metastatic malignant neoplasm with epithelial differentiation. The lymphoid component was not identified. The immunohistochemistry profile was positive for CAM 5.2, *PAX8*, and weakly positive for *CK7*. The tumor was negative for *CK20*, *CD10*, *TTF-1*, thyroglobulin, and RCC marker (Table 1). The immunoprofile was consistent with tumors such as renal cell carcinoma.

The diagnosis still was not entirely definitive based on this evaluation, and an unclassified renal cell carcinoma was the favored

Table 1. Immunohistochemistry markers

CAM 5.2	Broad marker for epithelial-derived tissues (liver, pancreas, GI tract, GU, renal tubules), hepatocellular carcinoma, and esophageal squamous cell carcinoma
PAX8	Expressed in clear cell, chromophobe, and papillary renal cell carcinomas; positive in thyroid and ovarian carcinomas
CK7	Found in most ductal, glandular, and transitional epithelium. Positive in lung, breast, thyroid, endometrium, ovarian, salivary gland, upper GI, urothelial, papillary renal cell, and transitional cell carcinomas
CK20	Positive in adenocarcinomas of colon, mucinous ovarian carcinomas, transitional cell, Merkel cell carcinomas; gastric, biliary system, pancreatic adenocarcinomas
CD10	Positive in B-lymphoblastic and Burkitt lymphomas, follicular lymphomas, some DLBCLs, multiple myelomas; breast myoepithelial cell, endometrial stromal sarcomas
TTF-1	Positive in lung and thyroid carcinomas
Thyroglobulin	Positive in thyroid carcinomas of papillary and follicular types
RCC marker (RCC Ma)	Positive in clear cell, papillary, chromophobe renal cell carcinomas; negative in other primary renal tumors. Of note, this is less commonly used due to lack of sensitivity and specificity, especially with the current utility of *PAX8*, *CAIX*, and *CD117*

Note. TTF = thyroid transcription factor; RCC = renal cell carcinoma; GI = gastrointestinal; GU = genitourinary; DLBCL = diffuse large B-cell lymphoma. Information from Neogenomics (n.d.); Pathology Outlines (n.d.).

diagnosis. However, as stated previously, the patient's mother noted that she has a history of sickle cell trait. History of sickle cell trait raised extreme concern for medullary renal cell carcinoma. Pathology was sent from the community hospital to a larger academic institution for review.

Follow-Up and Outcomes

Two days after the pathology initially resulted, the patient was transferred to a larger academic institution in anticipation of initiating chemotherapy if medullary renal cell carcinoma was confirmed on pathology review. Six days after he was transferred, his respiratory status decompensated requiring 80% to 90% high-flow nasal cannula, and he was ultimately intubated. That same day, final pathology review was complete, which revealed metastatic renal cell carcinoma, favoring medullary carcinoma. This was confirmed by the loss of *INI1/SMARCB1* expression, positive *OCT4*, and *PAX8* positivity. He was emergently started on chemotherapy with dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC). In the meantime, his hemoglobin electrophoresis resulted and revealed that he was positive for hemoglobin S trait, further supporting the suspicion of medullary renal cell carcinoma. Unfortunately, the patient continued to decompensate despite maximal ventilator support and pressors, with worsening hypoxia in the 70s and abrupt increase in bloody secretions. His family made the decision to transition to comfort care only and he was compassionately extubated, only 8 weeks after his initial symptoms started.

Renal cell carcinomas account for 2% to 3% of malignant neoplasms in adults (median age 64 years) but are rare in young adults less than 45 years old. Compared to older adults, young adults have a lower proportion of clear cell renal cell carcinoma (69% vs. 91%) and a higher incidence of chromophobe renal cell carcinoma, collecting duct carcinoma, and other rarer subtypes (Gopee-Ramanan et al., 2022).

Medullary renal cell carcinoma is exceedingly rare with fewer than 220 reported cases in the literature and is associated with sickle hemoglobinopathies (Beckermann et al., 2017; Davis et al., 1995; Ezekian et al., 2017). Cases are seen almost exclusively in those with sickle cell trait although a few cases have been reported in those with homozygous sickle cell disease. Medullary renal cell carcinoma is most often seen in young, African American men (ratio of 2:1) with the average age between 11 and 39 years. These patients usually present with flank pain, hematuria, and/or signs of metastatic disease, which may include respiratory symptoms such as cough and dyspnea, weight loss, decreased appetite, or bone pain. The right kidney is affected 75% more frequently than the left, and only about 5% present as localized disease. Medullary renal cell carcinoma cases comprise less than 0.5% of all renal cell carcinomas. To confirm the diagnosis, pathologists look for a loss of *INI1/SMARCB1* (Beckermann et al., 2017).

A diagnosis can be challenging as *INI1/SMARCB1* deficient tumors are diverse and typically have mixed phenotypes. In addition to medullary renal cell carcinoma, tumors with a complete loss of *INI1/SMARCB1* expression can include epithelioid sarcoma, atypical teratoid/rhabdoid tumor, myoepithelial carcinoma, malignant rhabdoid tumor, epithelioid malignant peripheral nerve sheath tumor, extraskeletal myxoid chondrosarcoma, chordoma, pancreas undifferentiated rhabdoid carcinoma, sinonasal basaloid carcinoma, and rhabdoid carcinoma of the gastrointestinal tract (Parker et al., 2020). Furthermore, renal cell carcinoma associated with anaplastic lymphoma kinase (*ALK*) gene rearrangement is another rare type of renal cell carcinoma that closely resembles medullary renal cell carcinoma as it arises from the medulla of the kidney and can also affect children or young adults with sickle cell trait. The key difference is that the *ALK* translocation renal cell carcinomas demonstrate intact *INI1/SMARCB1*, whereas medullary renal cell carcinomas demonstrate the loss of *INI1/SMARCB1* (Beckermann et al., 2017).

The histologic pattern for medullary renal cell carcinoma includes cribriform, reticular, cords, reminiscent of yolk sac tumor, tubular and solid

patterns within inflamed desmoplasia, and pleomorphism with frequent rhabdoid phenotype (Elliott & Bruner, 2019; Tretiakova, 2020). Unfortunately, fatality approaches 100% within several weeks to months after diagnosis, with a median survival of 4 months. Even with chemotherapy and surgery for localized disease, outcomes remain dismal, with a median survival of approximately 13 months. Given the aggressive nature of the disease, immediate platinum-based chemotherapy is needed (Beckermann et al., 2017).

The Renal Medullary Carcinoma (RMC) Working Group reviewed literature and developed clinical guidelines for standard treatment (Beckermann et al., 2017). For localized disease, a radical nephrectomy with retroperitoneal lymph node dissection is recommended. No adjuvant therapy has led to improved outcomes to date. In patients with a good performance status and low metastatic disease burden, the group recommends platinum-based chemotherapy either before or after debulking nephrectomy and retroperitoneal lymph node dissection.

Given the rarity of the disease, there is no general consensus for best frontline therapy. Clinical trials are often recommended if available. Typical frontline regimens that are utilized include platinum-based chemotherapy combination, such as dose-dense MVAC; or cisplatin/carboplatin and gemcitabine; or carboplatin with paclitaxel (Beckermann et al., 2017).

DISCUSSION

Due to the rarity of medullary renal cell carcinoma, the true incidence is unknown. Systemic treatment has been based upon case studies using regimens in renal cell carcinoma or urothelial carcinoma, but unfortunately, success has been minimal to date (Su & Hong, 2022). The loss of *INI1/SMARCB1* may be an essential feature for future directions for therapies. As previously noted, due to minimal success with standard of care chemotherapy, clinical trials are often recommended, if available. A current phase II clinical trial is testing the use of the EZH2 inhibitor tazemetostat (Tazverik) in adults with *INI1/SMARCB1*-negative tumors, which includes medullary renal cell carcinoma (NCT02601950). Another phase II clinical trial is exploring the use of the combination of nivolumab (Opdivo) and relatlimab (Opdualag) in locally advanced or metastatic medullary renal cell carcinoma (NCT05347212). Ixazomib (Ninlaro), gemcitabine, and doxorubicin are also being investigated in a phase II clinical trial in patients with locally advanced or metastatic medullary renal cell carcinoma (NCT03587662). Advanced practitioners can search on ClinicalTrials.gov to find available clinical trial options. Further research into effective treatment regimens, pathogenesis, and incidence is essential to improve outcomes in these patients.

CONCLUSION

Medullary renal cell carcinoma is an exceedingly rare, aggressive, and rapidly fatal disease. Unfortunately, there is no general consensus for frontline therapy. If clinical trials are not available for treatment, immediate platinum-based chemotherapy for metastatic disease is recommended. The advanced practitioner needs to be mindful of medullary renal cell carcinoma as a differential diagnosis when a young, African American patient with sickle cell trait presents with atypical local or metastatic renal cell carcinoma. Awareness of potential early signs of the disease in those with known sickle cell trait is crucial. It is imperative that the advanced practitioner address personal and family history with patients, including but not limited to solid tumor malignancies, blood disorders, and especially sickle cell trait and/or disease in the African American population. With the patient in this case, his mother's history of sickle cell trait was helpful in establishing the correct diagnosis. The purpose of this case study is to raise awareness and enhance education regarding this devastating disease.

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Disclosure

The author has no conflict of interest to disclose.

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