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Metastatic Renal Medullary Carcinoma: Case Report and Review of the Literature

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Abstract

Background: Renal medullary carcinoma (RMC) is a rare and aggressive renal tumor, typically affecting young patients with sickle cell trait. It is often diagnosed at a metastatic stage and is associated with a poor prognosis. **Case Presentation:** A 31-year-old male with no known hemoglobinopathy presented with macroscopic hematuria, right flank pain, and cachexia. Hemoglobin electrophoresis confirmed the absence of sickle-cell trait or disease. Imaging revealed a large right renal mass with extensive metastases to the liver, lymph nodes, peritoneum, lungs, and bone. Histopathological analysis and immunohistochemistry confirmed SMARCB1 (INI1)-deficient RMC. Baseline laboratory values at diagnosis were: creatinine 0.9 mg/dL, eGFR 95 mL/min/1.73 m^2, hemoglobin 10.5 g/dL, LDH 320 U/L, with ECOG performance status 1. First-line chemotherapy with cisplatin (75 mg/m^2, Day 1) and gemcitabine (1000 mg/m^2, Days 1 and 8) every 21 days resulted in disease progression after four cycles. Second-line therapy with paclitaxel (175 mg/m^2, Day 1) and zoledronic acid (4 mg IV, Day 1) every 21 days was initiated; the patient died after a single cycle. **Conclusion:** This case underscores the aggressive nature and poor therapeutic response of metastatic RMC. Diagnosis hinges on SMARCB1 loss, and outcomes remain poor despite systemic chemotherapy. Early recognition, accurate diagnosis, and referral to clinical trials are crucial for improving prognosis.

Keywords

Renal Medullary Carcinoma, Smarcb1-Deficient Carcinoma, Metastatic Renal Tumor, Hematuria, Young Adult, Cisplatin, Gemcitabine, Case Report

1. Background

Renal medullary carcinoma (RMC) is a highly aggressive and rare subtype of kidney cancer, accounting for less than 1% of all renal cell carcinomas. It is predominantly observed in individuals with sickle cell trait (SCT) or, less commonly, sickle cell disease (SCD), suggesting a direct oncogenic link to the hypoxic microenvironment of the renal medulla. RMC typically presents in young adults, often with advanced disease and distant metastases at diagnosis. Histologically, it is characterized by an infiltrative growth pattern, reticular or cribriform architecture, and a nearly universal loss of SMARCB1 (INI1) expression [1]. Given its rarity and aggressive nature, the prognosis remains poor, and effective therapeutic options are limited [2]. This case report describes a patient with metastatic RMC, discussing diagnostic challenges, clinical management, and outcomes.

2. Case Presentation

A 31-year-old male, former chronic smoker, presented with a three-month history of intermittent macroscopic hematuria and progressive right lumbar pain. He reported asthenia and cachexia. Initial work-up at an external clinic led to referral for comprehensive evaluation.

A thoraco-abdomino-pelvic CT scan revealed a large heterogeneous infiltrative mass in the lower pole of the right kidney, measuring 61 × 41 × 95 mm, with local invasion (contact with external oblique muscle and hepatic segment VI, invasion of inferior caliceal group). Extensive metastatic disease included:

- Confluent lymph node chain at the right renal hilum encasing the renal artery and vein.
- Multiple hypodense hepatic lesions, the largest 33 × 30 mm.
- Nodular lesions in the right greater peritoneal cavity (14.5 mm and 8.5 mm), suggestive of carcinomatosis.
- Low-abundance intraperitoneal effusion.
- Pulmonary micronodules in lower lobes.
- Mixed lesion in the left iliac wing, confirmed by bone scan.

Histopathology and immunohistochemistry confirmed SMARCB1 (INI1)-deficient renal carcinoma. Collecting-duct carcinoma and other SMARCB1-deficient tumors were excluded based on morphology and immunoprofile.

Treatment and Outcome

First-line chemotherapy with cisplatin (75 mg/m^2, Day 1) and gemcitabine (1000 mg/m^2, Days 1 and 8) every 21 days was administered for four cycles. Follow-up CT revealed progression of hepatic and bone metastases. The patient's performance status declined to WHO grade 2. A second-line regimen of paclitaxel (175 mg/m^2, Day 1) and zoledronic acid (4 mg IV, Day 1) every 21 days was initiated due to limited options and potential activity in metastatic RMC. Unfortunately, the patient died after a single cycle.

3. Discussion

Metastatic renal medullary carcinoma (RMC) remains one of the most aggressive and therapeutically challenging renal malignancies. Its rarity, aggressive biology, and frequent presentation at an advanced stage make early recognition difficult. In our patient, the disease was already widely metastatic at diagnosis, including hepatic, bone, pulmonary, and peritoneal involvement, consistent with reports that the majority of RMC cases are diagnosed at stage IV [1] [2].

RMC predominantly affects young adults, often in the third decade of life, contrasting with other renal cell carcinomas that more commonly affect older populations [3]. Its strong association with sickle cell trait (SCT) or, less commonly, sickle cell disease (SCD), is a defining feature of the disease [4] [5]. The pathophysiology involves chronic hypoxia and hyperosmolar stress in the renal medulla due to erythrocyte sickling. This microenvironment leads to microinfarctions, oxidative stress, and chronic inflammation, which are thought to contribute to malignant transformation of the collecting duct epithelium [6] [7].

Histopathologically, RMC is characterized by an infiltrative growth pattern with reticular, cribriform, or solid architecture, vesicular chromatin, and prominent nucleoli. Immunohistochemical loss of SMARCB1 (INI1) expression is considered pathognomonic [8]-[10]. In our case, alternative diagnoses such as collecting-duct carcinoma and other SMARCB1-deficient tumors were excluded based on a combination of morphology, immunoprofile (PAX8 positivity, CK7/CK19 patterns), and clinical context, reinforcing the specificity of the diagnosis [11] [12]. Accurate differentiation from these entities is essential, as management and prognosis differ.

Therapeutically, RMC is highly chemoresistant. Platinum-based regimens such as gemcitabine and cisplatin are commonly used first-line therapies, although responses are typically partial and short-lived [13]. In this patient, disease progression occurred despite four cycles of cisplatin/gemcitabine. The choice of paclitaxel combined with zoledronic acid as second-line therapy was informed by limited case series suggesting modest efficacy of paclitaxel in RMC, while zoledronic acid targets skeletal metastases and helps reduce skeletal-related events [13] [14]. Unfortunately, the patient did not respond, highlighting the urgent need for more effective therapies.

Recent advances in understanding the molecular landscape of RMC have identified potential therapeutic vulnerabilities. SMARCB1 loss creates synthetic lethality opportunities, with preclinical studies showing sensitivity to Aurora kinase inhibitors, proteasome inhibitors, EZH2 inhibitors, and PARP inhibitors [9]. Immunotherapy has also been explored; while RMC appears immunologically "cold" in most cases, select patients may benefit from checkpoint inhibitors. Clinical trials are ongoing, but evidence remains limited [13] [14].

Prognosis in RMC remains poor, with median overall survival ranging from 7 to 13 months for metastatic disease [4]. Factors influencing outcomes include disease stage, metastatic burden, performance status, and response to therapy. Early

recognition, histopathological confirmation, and rapid referral to specialized centers or clinical trials are critical steps to optimize patient care.

This case highlights the need for increased awareness among clinicians regarding RMC, particularly in young adults presenting with renal masses and hematuria. Incorporating SMARCB1 immunohistochemistry in the diagnostic work-up, careful staging, and consideration of clinical trial enrollment are essential strategies for improving outcomes in this highly aggressive disease.

4. Conclusion

Renal medullary carcinoma remains a devastating disease, characterized by its aggressive behavior, strong association with sickle cell trait, and high metastatic potential, particularly in young adults. This case report underscores the diagnostic challenges and the urgent need for improved therapeutic strategies. Increased awareness among clinicians, prompt and accurate diagnosis utilizing SMARCB1 immunohistochemistry, and robust participation in clinical trials are essential to advance our understanding and ultimately improve the dismal prognosis for patients with this challenging cancer.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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