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CASE REPORT

Atypical Presentation: A Clear Cell Carcinoma Case Diagnosed with Bone Marrow Metastasis

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ABSTRACT

Clear cell renal cell carcinoma (ccRCC) is the most common malignant neoplasm of the kidney. This tumor most frequently metastasizes to the lungs, bones, lymph nodes, and liver, respectively. However, bone marrow metastasis of ccRCC is extremely rare, with only a few cases reported in the literature. In this study, we present a case of ccRCC that initially manifested with bone marrow metastasis, leading to the diagnosis.

Keywords: Biopsy, bone marrow, carcinoma, hemophagocytic, leukemoid reaction, lymphohistiocytosis, renal cell

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INTRODUCTION

A 66-year-old male patient with no known chronic medical history presented to the emergency department with complaints of fever, back pain, fatigue, dyspnea, and nausea. On physical examination, he appeared cachectic and in poor general condition. His temperature was 37.8°C, and he exhibited tachycardia. A firm, slightly painful mass approximately 10 cm in size was palpated in the left lower abdomen. Decreased breath sounds were noted in the left lower hemithorax, with bilateral rales observed in the mid-zones. Informed consent was obtained.

Laboratory findings revealed neutrophilic leukocytosis (18.8×10^3/µL), elevated serum lactate dehydrogenase (LDH), and increased acute-phase reactants. Hemoglobin (Hb) was 14.3 g/dL, LDH was 975 U/L, C-reactive protein (CRP) was 239 mg/L, and INR was 1.26. Renal and hepatic function tests were within normal limits (Table 1 presents the laboratory characteristics).

Contrast-enhanced thoracic CT showed nodular lesions in the lungs, pleural effusion, and bilateral mosaic attenuation. Abdominal CT revealed a heterogeneous mass in the left kidney upper pole, approximately 12 cm in size, with central necrotic areas (Fig. 1).

The patient was hospitalized with presumptive diagnoses of pneumonia and malignancy. Although antibiotic therapy was initiated, fever and inflammatory markers continued to rise. A peripheral blood smear revealed a leukocytosis with a leukoerythroblastic picture. While ferritin levels showed a progressive increase during follow-up (rising from an initial value of 2.085 ng/mL to 8.832 ng/mL), fibrinogen levels demonstrated a downward trend, decreasing from 774 mg/dL to 398 mg/dL, in contrast to the increasing CRP levels. Diagnostic and therapeutic thoracentesis was performed, showing a transudative pleural effusion, and cytological examination revealed mesothelial cells and reactive lymphocytes.

As the patient's general condition worsened, and due to the presence of widespread metastatic disease, further diagnostic procedures could not be performed. Based on the available clinical and laboratory data, bone marrow aspiration and trephine biopsy were conducted with a pre-diagnosis of

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Table 1. Laboratory findings of the patient with references

Parameter*	Result	Reference range**
WBC (mm^3)	24.950	4.000–10.000 /mm^3
Neu (mm^3)	23.490	2.000–7.500 /mm^3
Hb (g/dl)/Hct (%)	11.8/38.9	Male: 13.5–17.5 g/dL/41–53%, Female: 12–16 g/dL/36–46%
MCV (fL)	86.4	80–100 fL
Plt (mm^3)	366.000	150.000–450.000 /mm^3
CRP (mg/dl)	257.02	<0.5 mg/dL
Ferritin (ng/mL)	8.532	Male: 30–400 ng/mL, Female: 15–150 ng/mL
Folate/Vit B12	2.9/131	Folate: 3–17 ng/mL, vit B12: 200–900 pg/mL
Na/K (mmol/L)	132/5.2	Na: 135–145 mmol/L, K: 3.5–5.1 mmol/L
BUN/Creatinine	26.52/0.82	BUN: 7–20 mg/dL, Creatinine: 0.6–1.3 mg/dL
AST/ALT (U/L)	265/94	AST: 5–40 U/L, ALT: 5–45 U/L
LDH (U/L)	2055	125–220 U/L
GGT/ALP (U/L)	568/684	GGT: 9–48 U/L, ALP: 44–147 U/L
Bilirubin (mg/dL)	0.81	0.2–1.2 mg/dL
PT/APTT (sec)	18.6/33.6	PT: 11–15 sec, APTT: 25–35 sec
Fibrinogen/D-dimer	398/4.4	Fibrinogen: 200–400 mg/dL, D-dimer: <0.5 µg/mL
ESR (mm/h)	121	Male: <15 mm/h, Female: <20 mm/h
Total Protein/Albumin (g/dL)	5.2/2.3	Total protein: 6.0–8.3 g/dL, Albumin: 3.5–5.0 g/dL

WBC: White blood cell; Neu: Neutrophil; Hb: Hemoglobin; HCT: Hematocrit; MCV: Mean corpuscular volume; Plt: Platelet; CRP: C-reactive protein; BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase; PT: Prothrombin time; APTT: Activated partial thromboplastin time; ESR: Erythrocyte sedimentation rate. Reference ranges are adapted from standard clinical biochemistry sources (Tietz Textbook of Clinical Chemistry and Molecular Diagnostics, 6th edition; Henry's Clinical Diagnosis and Management by Laboratory Methods, 23rd edition).

hemophagocytosis. The aspirate yielded a dry tap, and imprint smears showed rosette-like clusters of cells and an increased number of histiocytes (Fig. 2). Microscopic examination of hematoxylin and eosin-stained sections revealed a nodular infiltration composed of large, round cells with clear cytoplasm, prominent nucleoli, and centrally located nuclei. Subsequent immunohistochemical analysis showed that the infiltrative area was negative for MPO, CD61, and Glycophorin A, while it was positive for PanCK, PAX2, and Vimentin. The lesion was negative for CD10, Calretinin, RCC, EMA, WT-1, CK5/6, E-Cadherin, Cyclin D1, Bcl-2, CD3, CD20, CD30, and ALK1. In light of these findings, the case was diagnosed as a carcinoma metastasis. Considering the patient's clinical history of a renal mass, the morphological features of large round cells with clear cytoplasm, prominent nucleoli, and centrally located nuclei on hematoxylin and eosin staining, along with the immunohistochemical positivity for PanCK, PAX2, and Vimentin, the findings were interpreted as being most consistent with metastatic clear cell RCC (Fig. 3).

Empirical dexamethasone (4 mg/day) was initiated due to an HLH-like clinical presentation, along with supportive hemo-

Figure 1. The abdominal CT findings of the case are shown below. Abdominal CT demonstrating a 12 cm heterogeneous contrast-enhancing mass in the left renal fossa

CT: Computed tomography

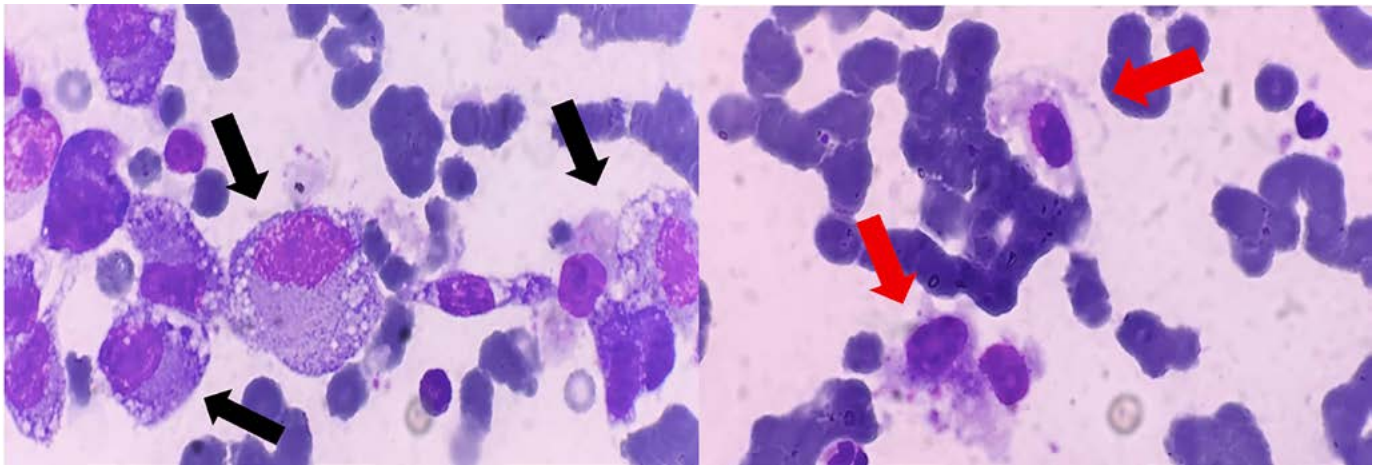

Figure 2. The bone marrow aspiration smear of the patient is depicted. Bone marrow aspiration smear showing large non-hematologic cells with clear cytoplasmic vacuoles (black arrows) and increased histiocytic activity (red arrows) (H&E, ×100)

static therapy. However, due to the development of respiratory failure, oncological treatment could not be administered, and intensive care support was started. Unfortunately, the patient passed away due to bacterial septicemia.

DISCUSSION

Solid organ neoplasms with bone marrow metastasis can dominate the clinical and laboratory findings through well-known mechanisms. First, if untreated, bone marrow metastasis may trigger hemophagocytic syndrome. Second, medullary narrowing and secondary reticulin fibrosis may also lead to myelofibrotic anemia.[1] The occurrence of bone marrow metastasis in clear cell renal cell carcinoma is extremely rare but can mimic hematological malignancies in laboratory findings.[2] In this case, the bone marrow infiltration presented with leukocytosis, anemia, elevated serum LDH, and fever, along with progressively increasing ferritin levels and a gradual decline in fibrinogen levels, contributing to the clinical picture. Therefore, considering the possibility of an HLH-like presentation in the differential diagnosis, and given that this presentation constitutes a life-threatening hematologic–immunologic emergency, early recognition and timely intervention were considered essential, and a bone marrow aspiration and biopsy were performed.

Renal cell carcinoma itself can cause fever, and in cases where pathological sampling from the primary tumor or distant metastases is not feasible, bone marrow sampling can provide a diagnostic solution.[3] Furthermore, RCC can induce a leukemoid reaction due to paraneoplastic granulocyte-colony stimulating factor (G-CSF) secretion, which, along with the hyperinflammatory state created by the disease, can lead to leukemoid reactions.[4]

In terms of oncopathological staging, solid organ neoplasms with bone marrow metastasis are classified as stage IV in the TNM staging system.[5] When advanced-stage cases reach a medically inoperable point, clinicians may alter their approach. This often results in the avoidance of invasive diagnostic procedures. Bone marrow aspiration and trephine biopsy can be valuable in such cases, as they are relatively simple bedside procedures that can be performed by appropriately trained clinicians involved in the patient's care.

The prognostic significance of bone marrow involvement has been well documented in the literature, as bone marrow micrometastases detected at diagnosis have been associated with poorer outcomes in several solid malignancies, particularly breast cancer, underscoring the importance of bone marrow evaluation from an oncological perspective.[6,7]

Reports of RCC with bone marrow metastasis are extremely rare in the literature. Whether this rarity is due to the infrequency of bone marrow metastasis itself or the academic community's tendency to undervalue case reports remains unclear. Furthermore, the assumption that there is no further action to be taken, coupled with the view that bone marrow aspiration and biopsy would not alter outcomes, likely contributes to their infrequent reporting.[8]

It is well known that most solid tumors can infiltrate bone marrow through micrometastasis, and this may lead to cytopenias, inflammatory processes, and hemophagocytosis.[9] Hematology specialists routinely consider bone marrow

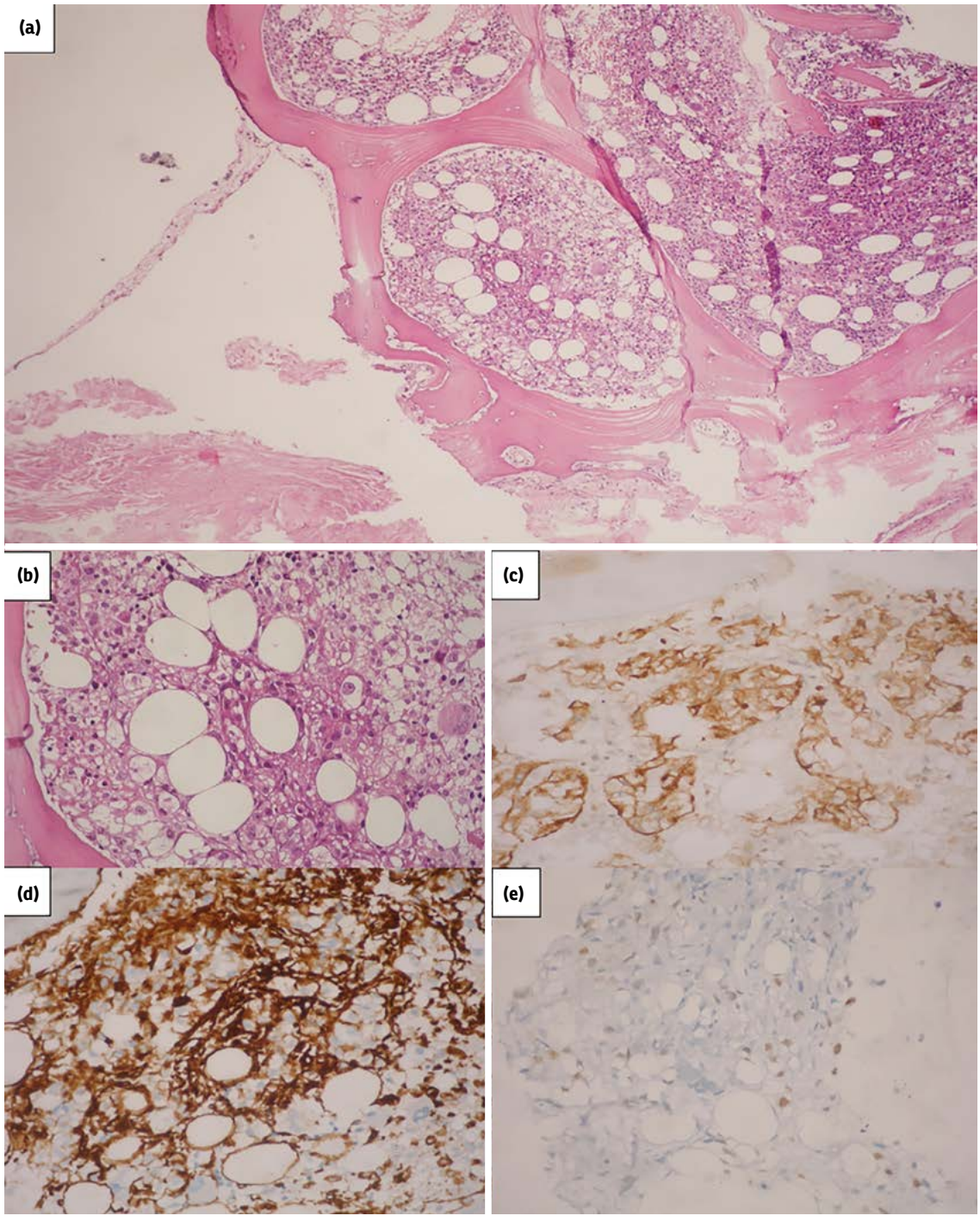

Figure 3. The immunohistochemical findings of the bone marrow trephine biopsy are shown. **(a)** Bone marrow trephine biopsy showing a paratrabecular infiltrate of large, round cells with clear cytoplasm and centrally located nuclei (H&E, ×10). **(b)** High-power view showing an infiltrate of large, round cells with clear cytoplasm, centrally located nuclei, and prominent nucleoli (H&E, ×40). **(c)** Immunohistochemical staining shows membranous positivity for PanCK in the large, round cells with clear cytoplasm and centrally located nuclei forming the nodule, whereas surrounding bone marrow cells remain negative (PanCK, ×40). **(d)** High-power immunohistochemical view showing suspicious membranous staining for vimentin in the large, round cells with clear cytoplasm and centrally located nuclei forming the nodule (Vimentin, ×40). E. High-power immunohistochemical view demonstrating nuclear positivity for PAX2 in the majority of cells forming the nodule (PAX2, ×40)

trephine biopsy in lymphoma cases for accurate clinical staging, especially in scenarios where disease refractoriness, transplant eligibility, or discordance with PET-CT findings may influence clinical management.[10] Therefore, for confirmed cases of malignancy, particularly when PET-CT fails to detect bone marrow infiltration, bone marrow aspiration and trephine biopsy are critical for accurate staging and management.

CONCLUSION

Bone marrow metastasis is a rare occurrence in renal cell carcinoma cases. In advanced-stage cases where the patient's condition deteriorates, and diagnostic procedures cannot be performed, bone marrow sampling should not be avoided, as it may provide a diagnostic solution. Bone marrow aspiration and biopsy remain valuable tools in the diagnostic workup of RCC with bone marrow involvement.

Disclosures

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent was obtained from the patient for publication of clinical information and images.

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