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(CASE REPORT)

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Renal collapse: A window into an underlying high-grade hematological malignancy – A case report

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Abstract

Kidney disease is prevalent in patients with hematologic malignancies, particularly multiple myeloma (MM) and acute leukemias. These conditions can directly infiltrate the kidneys or disrupt renal function through metabolic and immunological mechanisms. Renal failure is a significant complication, often the second leading cause of mortality in MM patients. Over 50% of multiple myeloma patients experience renal impairment, commonly identified as "myeloma kidney." Occasionally, blastoid morphology of some plasma cells can lead to diagnostic confusion, necessitating the use of immunohistochemistry to distinguish plasma cell leukemia (PCL) from other types of leukemias and lymphomas. Accurate diagnosis of renal disease can also reveal underlying hematologic malignancies, as demonstrated in our case where a kidney biopsy diagnosed a high-grade malignancy, facilitating timely and correct management.

Keywords: Plasma cell leukemia; Cast nephropathy; Kidney biopsy; Blast cells; Chemotherapy

1. Introduction

Kidney disease is common among patients with hematologic malignancies and can affect various kidney compartments, including the vasculature, tubules, interstitium, and glomeruli. Hematological malignancies (HMs), particularly multiple myelomas (MMs), leukemias, and lymphomas, are the most common non-renal tumors impacting kidney function. They can directly infiltrate the kidneys or impair renal function through various metabolic and immunological changes[1]. Vascular issues can arise from both microvascular and macrovascular damage due to conditions like thrombotic microangiopathy, hyperleukocytosis, hyperviscosity, and cryoglobulinemia. The tubulointerstitial compartment can experience problems such as prerenal azotemia and acute tubular injury. In specific populations, it's important to consider additional factors like malignant infiltration, tumor lysis syndrome, cast nephropathy, granulomatous interstitial nephritis, and lysozymuria[2]. In many cases, the rapid and accurate diagnosis of the renal disease helps unmasking the underlying hematological malignancy. Here, we represent an interesting case of renal failure where a kidney biopsy helped diagnose a high-grade hematological malignancy and thus resulted in early initiation of the management for the patient.

2. Case report

A 58-year-old male with no known co-morbidities was referred from a peripheral center with the chief complaints of:-

- Easy fatiguability and shortness of breath on exertion for the last 1 month
- Decreased urine output associated with nausea and abdominal pain for the last 1 week.

The onset of the above-mentioned symptoms was insidious. The pain in the abdomen was dull aching in nature and non-localised. There was no associated fever, loose stools, or burning micturition. There was no significant past or

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medical history. Laboratory investigations at the peripheral center revealed severe anemia with a deranged kidney function test: Urea/Creatinine of 68/2.1 mg/dl.

On examination: The patient was conscious and oriented to time, place, and person. His vitals were stable. He had severe pallor and a pitting type of bilateral pedal edema. The systemic examination was unremarkable except for hepatomegaly with a liver span of 17 cm. Routine investigations were sent which are shown in Table 1.

Table 1 Initial Investigations

Parameters	Values	Parameters	Values
HB	5.9 gm/dl	Na/K	138/4.6 mmol/l
Haematocrit	18.8%	Ca/PO4	10.2/4.5 mg/dl
TLC	2900 mm^3	TB/DB	1.2/0.6 mg/dl
DLC	67/24/5/2	AST/ALT/ALP	56/68/122 U/L
Platelet count	1.01 L	TP/SA	9.2/2.6 g/dl
Urine microscopy	Normal	Urea/ creatinine	102/5.3 mg/dl

HB- hemoglobin, Hct- hematocrit, TLC- total leucocyte count, DLC- differential leucocyte count, TP- Total protein, SA- serum albumin, AST- aspartate aminotransferase, ALT- alanine aminotransferase, ALP- alkaline phosphatase, TB- total bilirubin, DB- direct bilirubin, Na- Sodium, K- Potassium, Ca- Calcium, PO4- Phosphate

- Peripheral smear: Normocytic normochromic anemia with few microcytes with **38% atypical blast cells of myeloid lineage** with the **possibility of acute myeloid leukemia.**
- CXR: Normal study
- ECG: Sinus tachycardia.
- USG W/A: **Hepatosplenomegaly**, bilateral kidneys of normal size with CMD maintained and raised cortical echo
- Arterial blood gas analysis: - metabolic acidosis

2.1. Provisional diagnosis

Pancytopenia in the background of hematological malignancy with Rapidly progressive renal failure (? Etiology)

Further workup was sent in view of rapidly progressive renal failure which is summarised in Table 2.

Table 2 Workup for Rapidly progressive renal failure

Parameters	Values	Parameters	Values
Iron/TIBC	78/322 mcg/dl	24-hour urinary protein	3.4 gm/day
Ferritin	678 ng/ml	UFAS	Inactive sediments with no RBC casts
B12	566 pg/ml	HIV	Non-reactive
Folate	4.8 ng/ml	HbsAg/ Anti-HCV	Non-reactive
TFT	Normal	ANA/ Anti dsDNA/ ANCA/ Anti GBM	Negative
HBA1C	5.6%	C3/C4	Normal

TFT- thyroid function test, UFAS- urine for active sediments, HIV- human immunodeficiency virus, HBsAg- Hepatitis B surface antigen, HCV- hepatitis C virus, ANA- anti-nuclear antigen, ANCA, anti-nuclear cytoplasmic antibody, GBM- Glomerular basement membrane, TIBC- total iron binding capacity, C3/C4- complement protein 3/4

2.2. Course

The patient had rapidly progressive deteriorating renal function with oliguria and was stabilized initially with high-dose steroids and hemodialysis. Once the patient was stabilized, a kidney biopsy and a bone marrow biopsy were planned. Meanwhile, Serum protein electrophoresis (SPEP)/Urine protein electrophoresis (UPEP) and serum-free light chain assays were also sent.

2.2.1. Kidney biopsy revealed Light chain cast myelopathy

It was suspected that there is a co-existence of multiple myeloma and AML in this patient.

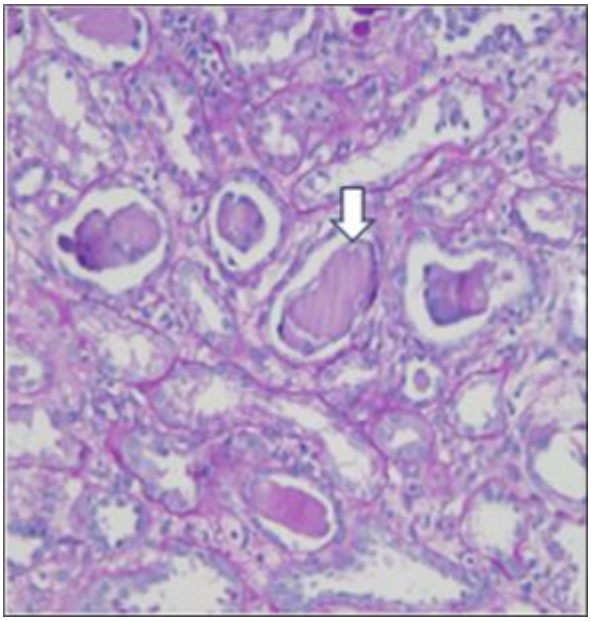

Figure 1 Light chain cast nephropathy – Arrow showing eosinophilic homogenous casts inside renal tubules

However, the bone marrow examination revealed 56% plasma cells with 38% plasma cells in circulating blood, which were misidentified as blasts on the initial smear**.** Hence, a revised diagnosis of Plasma cell leukemia causing RPRF as a result of light chain cast myelopathy was made with SPEP revealing monoclonal gammopathy with M spike and raised serum free light chain assay.

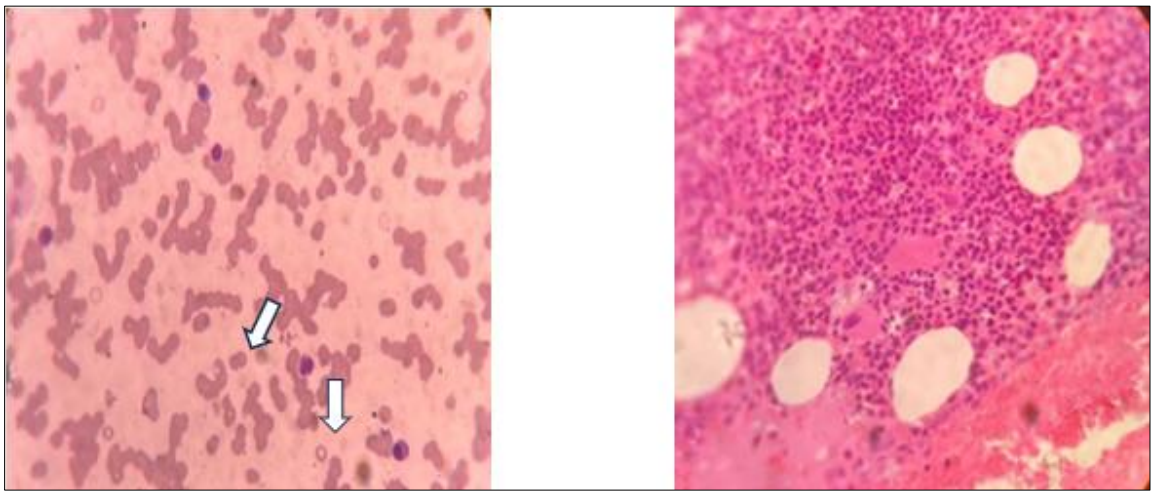

Figure 2 Plasma cells on peripheral smear and bone marrow

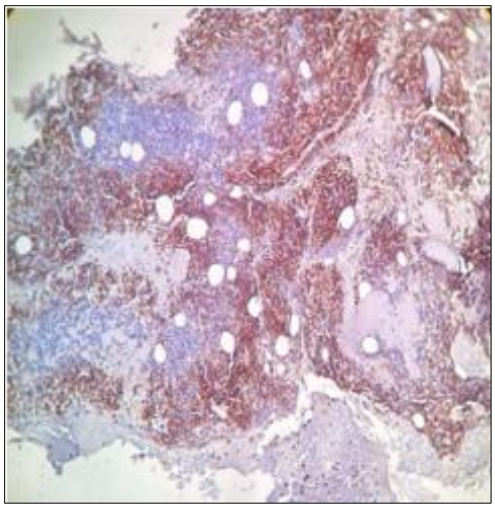

Figure 3 Plasma cells positive for CD38

After 8 sessions of hemodialysis and conservative management, the patient's KFT improved to **48/1.8.** The patient was then referred to a hemato-oncologist for initiation of chemotherapy.

3. Discussion

Multiple myeloma (MM) is a clonal malignancy of plasma cells that accounts for about 10% of hematologic cancers. Plasma cell leukemia (PCL) is an aggressive variant of multiple myeloma marked by the uncontrolled clonal proliferation of plasma cells (PCs) in both the bone marrow and peripheral blood. As per the recently updated International Myeloma Working Group consensus definition in December 2021, the diagnosis of primary PCL is defined by the presence of 5% or more plasma cells in peripheral blood smear (used to be ≥ 20% previously) in patients otherwise diagnosed with symptomatic MM[3]. Sometimes, these plasma cells can be confused with blast cells in peripheral blood, especially those with blastoid morphology. It is classified into two types: primary PCL, which arises de novo, and secondary PCL, which occurs in the later, advanced stages of multiple myeloma (MM)[4]. The median age for diagnosis is 66 years, making it primarily a disease of older adults.

Table 3 Spectrum of renal diseases associated with Plasma cell Leukemia[6]

S No.	Renal manifestation of myeloma group of disorders
1.	Myeloma kidney or cast nephropathy
2.	Light-chain deposition disease (LCDD)
3.	Renal tubular dysfunction
4.	Fibrillary glomerulonephritis
5.	Immunotactoid glomerulopathy
6.	Type I cryoglobulinemia
7.	Proliferative glomerulonephritis with monoclonal IgG deposits
8.	C3 glomerulopathy with monoclonal gammopathy
9.	Renal crystallopathies
10.	Effects of hypercalcemia

One of the major complications of Plasma cell leukemia is renal involvement. Renal failure is the second most common cause of mortality in patients with multiple myeloma, second only to infections. More than 50% of Multiple myeloma patients experience renal failure, often due to a condition known as myeloma kidney[5]. Several parameters are linked to renal failure (RF), but logistic regression analysis indicated that renal failure is independently associated only with

the International Staging System and Bence Jones proteinuria. The presence of renal failure showed a trend toward a higher early death rate, although the response to primary therapy was similar. Patients with renal failure had a median survival of 19.5 months, compared to 40.4 months for those without renal failure [5].

Cast nephropathy is by far the most common renal disease associated with multiple myeloma, found in 40% to 60% of renal biopsies in patients with multiple myeloma and kidney disease. The normal level of light chain excretion is less than 30 mg per day. However, in multiple myeloma, excess light chain production can surpass the kidney's reabsorptive capacity, resulting in increased excretion that can range from 100 mg to over 20 g per day. This leads to the accumulation of light chains due to elevated excretion rates, resistance to degradation, and saturation of the endocytosis process. These light chains can release proinflammatory cytokines and reactive oxygen species, damaging the proximal tubules and inducing apoptosis. Light chain cast nephropathy is regarded as a "myeloma-defining event" and may either be the initial presentation of multiple myeloma or develop later during the disease progression[7]. On histopathology, this condition is marked by dense, eosinophilic, homogeneous casts that are often laminated or fractured and are typically accompanied by multinucleated giant cells resembling foreign body reactions. Cast nephropathy starts in the collecting tubules, so biopsy samples should include some medullary tissue[8].

Evaluation of myeloma kidney includes serum and urine protein electrophoresis with immunofixation, urinalysis, and kidney biopsy. It's important to note that serum electrophoresis (SPEP) often fails to detect M-protein levels below 500 mg/dL, particularly when the M-protein consists of free light chains, which have a shorter half-life than intact immunoglobulins. One study found that serum electrophoresis did not identify M-protein abnormalities in over 50% of AL amyloidosis cases. Serum-free light chain assays utilize antibodies that target exposed antigens of serum-free light chain, excluding intact immunoglobulins, making them more sensitive than serum electrophoresis [9]. Cast nephropathy generally presents with proteinuria without albuminuria, as the glomerular basement membrane (GBM) remains intact. A presumptive diagnosis of light chain cast nephropathy can be made when multiple myeloma is accompanied by acute kidney injury (AKI) or subacute kidney injury, characterized by a serum-free light chain concentration of ≥1500 mg/L and a predominance of monoclonal light chains in the urine as indicated by urine protein electrophoresis and immunofixation. In our case, along with proteinuria without albuminuria, a kidney biopsy helped establish the diagnosis of myeloma kidney.

The initial treatment for patients with myeloma-associated kidney diseases should prioritize evaluating the extent of renal impairment and addressing hemodynamic status, volume status, and electrolyte imbalances. Additionally, it is important to minimize the formation of casts and reduce paraprotein concentration as early as possible. About 80% of patients may recover renal function by 3 weeks if there is a reduction in the serum-free light chains by at least 60%[6]. This can be achieved with the early initiation of chemotherapy. The commonly used treatment regimens for multiple myeloma include:

- Cyclophosphamide, bortezomib, and dexamethasone (CyBorD)
- Lenalidomide and dexamethasone (Rd)
- Lenalidomide, bortezomib, and dexamethasone (RVD)
- Lenalidomide, thalidomide, and dexamethasone (VTD)

Plasma exchange or plasmapheresis can effectively reduce paraprotein concentrations. High-cutoff hemodialysis (HCO-HD) is another method for extracorporeal removal of free light chains (FLCs) based on their molecular weight. One randomized controlled trial compared patients with myeloma cast nephropathy who were treated with bortezomib and dexamethasone, followed by intensive dialysis with either a high-cutoff dialyzer or a conventional dialyzer. While the number of patients who became dialysis-independent was higher in the high-cutoff group, the difference did not reach clinical significance, possibly due to the small sample size. A critical factor associated with dialysis independence was achieving a serum-free light chain level of less than 500 mg/dL after the initial chemotherapy, which is the threshold for cast formation[10].

4. Conclusion

- Plasma cell leukemia is an aggressive hematological malignancy with renal involvement in up to 50% of cases.
- Many times, renal failure is the first presentation of such a disease and hence the algorithmic approach to rapidly progressive renal failure helps unmasquerading the underlying malignancy
- Plasma cell leukemia with blastoid morphology can pose a diagnostic challenge by mimicking acute leukemia as was seen initially in our case. Renal involvement in this case clarified the diagnostic dilemma between the diseases, allowing for a distinct approach to management.

- This case underscores the significance of the emerging field of onco-nephrology and emphasizes the necessity for a collaborative approach involving hematologists, pathologists, and oncologists to provide comprehensive care for patients with complex clinical presentations.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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