



Spectrum of Renal Manifestations in Hematological Malignancies

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Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

Abstract

Background: Hematological malignancies frequently exert profound effects on renal function through a variety of direct and indirect mechanisms. The kidney, as both a target and participant in systemic disease, reflects the complex interplay between malignant hematopoietic cells, immune dysregulation, and metabolic disturbances. Renal manifestations in hematologic malignancies encompass a wide spectrum ranging from asymptomatic biochemical abnormalities to severe acute kidney injury (AKI), chronic kidney disease (CKD), and nephrotic or nephritic syndromes. The pathophysiological underpinnings involve glomerular deposition of immunoglobulins and paraproteins, tubular injury from light chains or chemotherapeutic agents, and interstitial or vascular involvement by infiltrating malignant cells.

The clinical presentation of renal disease in these patients is highly heterogeneous, often masking or mimicking other systemic or primary renal disorders. Early identification and accurate diagnosis are crucial since renal dysfunction significantly impacts therapeutic decisions, chemotherapy dosing, and overall survival. The emergence of the multidisciplinary field of **onconeurology** underscores the importance of integrated care for these complex cases. However, diagnostic challenges remain substantial due to overlapping clinical features, the need for invasive biopsy procedures, and the limitations of current biomarkers in differentiating between drug-induced and disease-related injury.

This review aims to delineate the **clinical spectrum and pathophysiological mechanisms** of renal involvement in hematologic malignancies, emphasizing the diagnostic dilemmas and highlighting recent advances in understanding these processes. By integrating current evidence, it seeks to aid clinicians in recognizing renal manifestations early, interpreting laboratory and histological findings appropriately, and optimizing patient outcomes through timely intervention and multidisciplinary collaboration. Ultimately, greater clarity in the renal–hematologic interface will foster improved strategies for both diagnosis and management, bridging an important gap in contemporary internal medicine.

Keywords: Renal Disease, Hematological Malignancies, Pathophysiological Insights



Introduction

Renal involvement in hematological malignancies represents one of the most challenging intersections between nephrology and hematology. Both organ systems are tightly interrelated, as the kidney is responsible for maintaining metabolic homeostasis and filtering byproducts generated by abnormal hematopoietic activity. In patients with hematological cancers—including multiple myeloma, lymphomas, leukemias, and myeloproliferative disorders—renal disease is not only common but often dictates prognosis and therapeutic strategy. Estimates suggest that between **20% and 60%** of patients with hematological malignancies experience some degree of renal impairment during their disease course, either from the malignancy itself or from its treatment [1].

The pathogenesis of kidney injury in this context is multifactorial. It may result from **direct infiltration** of malignant cells into renal tissue, **immune complex-mediated glomerulopathies**, **paraprotein deposition**, or **nephrotoxic effects** of chemotherapeutic agents. Systemic complications such as tumor lysis syndrome, hypercalcemia, and infection also play critical roles in precipitating or aggravating renal dysfunction. As these processes overlap and evolve dynamically with disease progression, clinicians face substantial diagnostic and therapeutic uncertainty [2].

The **clinical presentation** of renal disease in hematological malignancies is notably diverse, ranging from asymptomatic proteinuria to life-threatening renal failure. In many cases, renal abnormalities may be the **first manifestation** of an underlying hematologic malignancy, preceding its hematologic diagnosis by weeks or months. This makes early recognition crucial for initiating targeted evaluation and therapy. Unfortunately, renal biopsy—the gold standard for diagnosis—is not always feasible due to thrombocytopenia, coagulopathy, or patient instability [3].

Despite the growing awareness of **onconeurology**, the field still suffers from a lack of standardized diagnostic algorithms and validated biomarkers. Most studies remain retrospective or disease-specific, leaving significant **research gaps** in understanding the true incidence, prognostic significance, and optimal management of renal involvement across different hematologic malignancies [4].

The present review aims to synthesize current knowledge on the **pathophysiological mechanisms, clinical manifestations, and diagnostic approaches** to renal disease in hematological malignancies. It highlights the challenges clinicians face in differentiating between malignancy-related and therapy-induced injury, discusses disease-specific renal syndromes, and explores future directions for research and patient care [5].

Pathophysiological Insights

The pathophysiology of renal involvement in hematological malignancies is complex and multifactorial, involving direct infiltration, immune-mediated injury, metabolic disturbances, and treatment-related nephrotoxicity. The kidney can be affected by malignant cells themselves, circulating paraproteins, or cytokine-mediated inflammatory cascades. Each mechanism reflects a distinct biological process, yet many coexist in a single patient, leading to overlapping clinical and pathological presentations [6].

2.1 Direct Infiltration and Structural Involvement

Renal infiltration by malignant hematopoietic cells is a hallmark in some leukemias and lymphomas. Infiltrating cells may occupy the interstitial, peritubular, or glomerular compartments, leading to increased renal size, parenchymal compression, and compromised function. Acute kidney injury (AKI) may occur secondary to this infiltration, especially in aggressive lymphomas or acute leukemias with high tumor burden. Histologically, infiltration manifests as dense cellular aggregates causing tubular atrophy and interstitial edema, often without overt glomerular involvement. Clinical features include proteinuria, mild hematuria, and progressive renal dysfunction, sometimes accompanied by flank pain or renal enlargement detectable on imaging [7].

2.2 Paraprotein and Immunoglobulin-Mediated Injury

In plasma cell dyscrasias and B-cell malignancies, monoclonal immunoglobulins or light chains cause direct renal injury through deposition and aggregation. These proteins can precipitate in renal tubules,



forming casts that obstruct flow and elicit inflammation—a condition known as **myeloma cast nephropathy**. Alternatively, they may deposit within glomeruli, producing light-chain deposition disease (LCDD) or amyloidosis. Such deposition alters glomerular permeability, resulting in heavy proteinuria and nephrotic syndrome. In many cases, free light chains induce oxidative stress and activate complement pathways, aggravating tubular injury and fibrosis [8].

2.3 Immune Complex and Complement Activation

Immune dysregulation in hematologic malignancies promotes the formation of circulating immune complexes composed of tumor antigens and antibodies. These complexes deposit in glomeruli and trigger complement activation, leading to glomerulonephritis resembling membranoproliferative or lupus-like patterns. Chronic activation of the classical and alternative complement pathways induces glomerular inflammation and endothelial injury. In lymphoproliferative disorders, monoclonal cryoglobulinemia can develop, leading to cryoglobulinemic vasculitis and glomerular deposition of immunoglobulins, fibrin, and complement components [9].

2.4 Cytokine and Growth Factor Dysregulation

Malignant hematopoietic cells often secrete a variety of cytokines—such as interleukin (IL)-6, tumor necrosis factor- α , and vascular endothelial growth factor—that promote renal injury. IL-6, in particular, stimulates mesangial proliferation and increases glomerular permeability, while VEGF induces endothelial dysfunction and microvascular leakage. These pathways contribute to paraneoplastic glomerular diseases, including minimal change disease and membranous nephropathy, observed in association with Hodgkin and non-Hodgkin lymphomas. The inflammatory milieu further amplifies oxidative stress and tubular apoptosis, accelerating chronic kidney injury [10].

2.5 Metabolic and Hemodynamic Factors

Metabolic disturbances such as hypercalcemia, hyperuricemia, and hyperphosphatemia frequently accompany hematologic malignancies and contribute to kidney damage. Tumor lysis syndrome, resulting from rapid tumor cell breakdown after chemotherapy or spontaneously in high-grade malignancies, leads to uric acid and calcium phosphate crystal deposition in renal tubules. These deposits cause obstruction and inflammation, resulting in oliguric AKI. Hypercalcemia—common in multiple myeloma and adult T-cell leukemia—induces vasoconstriction, natriuresis, and nephrocalcinosis, compounding renal impairment [11].

2.6 Drug-Related and Treatment-Induced Nephrotoxicity

Chemotherapeutic agents, targeted therapies, and supportive drugs can significantly exacerbate renal injury. Cisplatin, ifosfamide, and methotrexate are well-known nephrotoxins, while newer agents such as proteasome inhibitors (e.g., bortezomib) and monoclonal antibodies may cause thrombotic microangiopathy or interstitial nephritis. Hematopoietic stem cell transplantation introduces additional risks, including graft-versus-host disease-associated nephropathy and calcineurin inhibitor toxicity. These mechanisms often act synergistically with malignancy-related injury, complicating attribution and management [12].

2.7 Interstitial and Vascular Pathology

The renal interstitium and vasculature frequently serve as sites of injury in hematologic malignancies. Interstitial nephritis can occur due to leukemic infiltration, cytokine-mediated inflammation, or hypersensitivity reactions to drugs. Vascular injury may manifest as thrombotic microangiopathy, characterized by endothelial swelling, fibrin deposition, and microthrombi formation—commonly associated with chemotherapy or transplant conditioning regimens. Vascular compromise further perpetuates ischemic tubular injury and glomerulosclerosis, leading to progressive CKD [13].

In summary, the renal pathophysiology in hematologic malignancies involves a dynamic interplay between **malignant infiltration, immune dysregulation, paraprotein deposition, and metabolic injury**. Understanding these overlapping mechanisms is essential for interpreting renal findings and tailoring treatment strategies to prevent irreversible damage.

3. Spectrum of Renal Involvement



The renal involvement in hematological malignancies spans a wide clinicopathological spectrum, affecting glomeruli, tubules, interstitium, and vasculature. This diversity reflects the multiplicity of mechanisms underlying renal injury, ranging from immune complex deposition to direct tumor cell infiltration and treatment-induced toxicity. Clinically, these manifestations can vary from subclinical abnormalities detected only on laboratory testing to fulminant renal failure requiring dialysis. The ability to recognize this spectrum is essential for timely diagnosis and targeted management, as the renal presentation often mirrors the underlying hematologic disorder's biology and stage [14].

3.1 Glomerular Disease Spectrum

Glomerular lesions are common in patients with hematological malignancies and are often immune-mediated or paraprotein-associated. **Membranoproliferative glomerulonephritis (MPGN)** frequently develops in chronic lymphocytic leukemia and lymphomas due to deposition of immune complexes and complement activation. Similarly, **minimal change disease (MCD)** and **membranous nephropathy (MN)** are reported in Hodgkin and non-Hodgkin lymphomas as paraneoplastic phenomena, likely mediated by cytokines such as interleukin-13 and tumor necrosis factor- α . In plasma cell dyscrasias, glomerular involvement is dominated by **light-chain deposition disease** and **amyloidosis**, which cause nephrotic-range proteinuria, hypoalbuminemia, and progressive renal impairment. Histopathologically, these entities exhibit mesangial expansion, double-contoured basement membranes, and characteristic immunoglobulin deposits visible on electron microscopy [15].

3.2 Tubular and Tubulointerstitial Lesions

Tubular injury is a major contributor to renal dysfunction in hematological malignancies, particularly in multiple myeloma and acute leukemia. In **myeloma cast nephropathy**, excessive free light chains precipitate in distal tubules, forming obstructive casts that incite inflammation and tubular necrosis. Interstitial nephritis may occur secondary to leukemic infiltration, cytokine-induced inflammation, or hypersensitivity to chemotherapeutic agents. Chronic tubulointerstitial changes manifest as atrophy, fibrosis, and impaired concentrating ability, leading to persistent polyuria or renal tubular acidosis. Functionally, tubular involvement often presents with disproportionate azotemia relative to proteinuria, and biopsy reveals a mixed picture of degeneration, interstitial edema, and inflammatory infiltrates [16].

3.3 Interstitial Infiltration by Malignant Cells

Direct infiltration of the kidney by malignant hematopoietic cells is observed most often in **acute lymphoblastic leukemia (ALL)**, **acute myeloid leukemia (AML)**, and **high-grade lymphomas**. Clinically, it can present as acute renal failure, nephromegaly, or unexplained proteinuria. Radiological imaging may show enlarged, hypodense kidneys without obstruction, while biopsy confirms the presence of atypical lymphoid or myeloid cells in the interstitium. The extent of infiltration often correlates with disease burden and prognosis. Effective cytoreductive therapy typically results in partial or complete renal recovery, highlighting the importance of distinguishing this entity from drug-induced nephrotoxicity [17].

3.4 Vascular and Microangiopathic Involvement

Vascular pathology in hematologic malignancies manifests as **thrombotic microangiopathy (TMA)**, **vasculitis**, or **hyperviscosity-related injury**. TMA can arise from malignant endothelial damage, chemotherapeutic agents such as gemcitabine or mitomycin-C, or after hematopoietic stem cell transplantation. Pathologically, it is characterized by endothelial swelling, fibrin deposition, and glomerular capillary thrombosis, leading to microangiopathic hemolytic anemia and renal ischemia. Hyperviscosity syndromes, common in Waldenström macroglobulinemia and multiple myeloma, cause sluggish blood flow and vascular occlusion, resulting in hypoperfusion and cortical necrosis. Vasculitic lesions, though rare, may develop due to immune complex deposition or paraneoplastic mechanisms, adding further complexity to renal pathology [18].

3.5 Spectrum of Clinical Severity

The clinical spectrum of renal disease ranges from mild, transient laboratory abnormalities to advanced renal failure. Some patients exhibit isolated **microscopic hematuria or subnephrotic proteinuria**,



while others develop **nephrotic syndrome** or **rapidly progressive glomerulonephritis**. **Acute kidney injury (AKI)** occurs in 10–30% of patients with hematologic malignancies, whereas **chronic kidney disease (CKD)** develops insidiously in those with sustained metabolic or paraprotein-related injury. The overlap between malignancy-related and therapy-induced lesions complicates management decisions and requires careful histopathological correlation. Importantly, the pattern and tempo of renal involvement often mirror the underlying hematologic process—acute in leukemias and lymphomas, indolent in plasma cell disorders [19].

3.6 Overlap and Mixed Pathologies

In many patients, renal biopsy reveals **mixed pathologies**, such as concurrent glomerular immune complex disease and tubular cast nephropathy or infiltration combined with interstitial nephritis. This overlap underscores the multifaceted mechanisms operating simultaneously in hematological malignancies. Such cases are particularly challenging diagnostically, as they require careful interpretation of renal histology, immunofluorescence, and clinical context. Understanding the interplay between these mechanisms is key to devising rational treatment strategies, balancing cytoreduction with renal protection, and minimizing therapeutic nephrotoxicity [20].

Taken together, the renal spectrum in hematological malignancies is broad and often multifactorial, emphasizing the need for multidisciplinary assessment and individualized management. Recognition of the specific renal lesion type provides crucial insights into disease activity, prognosis, and therapeutic options.

4. Clinical Manifestations

The clinical presentation of renal involvement in hematological malignancies is diverse, reflecting the multiplicity of pathogenic mechanisms affecting different compartments of the kidney. Manifestations range from asymptomatic biochemical derangements to fulminant renal failure with systemic complications. Recognizing these patterns is essential because renal symptoms may precede, coincide with, or follow the diagnosis of hematological malignancy, and their onset often provides important diagnostic or prognostic clues [21].

4.1 Acute Kidney Injury (AKI)

Acute kidney injury is one of the most frequent and clinically significant renal presentations in hematologic malignancies. It may develop abruptly due to tumor lysis syndrome, tubular obstruction from myeloma casts, leukemic infiltration, or drug-induced nephrotoxicity. In **tumor lysis syndrome**, massive tumor cell breakdown releases uric acid, phosphate, and potassium, leading to crystal precipitation within tubules and metabolic disturbances such as hyperuricemia and hyperkalemia. Myeloma cast nephropathy, another classic cause of AKI, occurs when free light chains obstruct tubular lumina and incite inflammatory injury. Patients typically present with rapid increases in serum creatinine, oliguria, and electrolyte abnormalities. Early detection and prompt management with hydration, uric acid-lowering therapy, and control of tumor burden are vital for preventing irreversible renal failure [22].

4.2 Chronic Kidney Disease (CKD)

Chronic kidney disease represents the cumulative effect of prolonged renal injury from paraprotein deposition, infiltration, or treatment toxicity. CKD often develops insidiously, manifesting as fatigue, anemia, and gradual rise in creatinine levels. In multiple myeloma and Waldenström macroglobulinemia, chronic tubular and glomerular injury leads to progressive loss of nephron mass and irreversible fibrosis. Persistent hypercalcemia and recurrent AKI episodes accelerate this decline. CKD in hematologic malignancies portends a poorer prognosis, limiting the use of nephrotoxic chemotherapeutics and complicating bone marrow transplantation protocols [23].

4.3 Proteinuria and Hematuria

Proteinuria, either in the nephrotic or subnephrotic range, is a frequent marker of glomerular involvement. In **light-chain deposition disease** and **amyloidosis**, massive albuminuria occurs due to



disruption of the glomerular basement membrane. Nephrotic-range proteinuria (>3.5 g/day) may present with edema, hypoalbuminemia, and dyslipidemia, mimicking primary nephrotic syndromes. Hematuria, whether microscopic or macroscopic, arises from glomerular inflammation, vascular lesions, or infiltration. When hematuria is accompanied by dysmorphic red cells or red cell casts, glomerulonephritis should be suspected. Importantly, new-onset proteinuria or hematuria in a patient with hematologic malignancy may signal disease relapse or transformation [24].

4.4 Nephrotic Syndrome

Nephrotic syndrome is a characteristic feature of several hematologic-associated renal disorders, including **amyloidosis**, **minimal change disease**, and **membranous nephropathy**. These conditions manifest with massive proteinuria, hypoalbuminemia, and peripheral edema. In amyloidosis secondary to plasma cell dyscrasia, renal involvement is often the dominant feature, with progressive proteinuria leading to renal failure if untreated. Paraneoplastic nephrotic syndromes linked to Hodgkin lymphoma tend to respond to chemotherapy targeting the underlying malignancy, supporting an immune-mediated mechanism. Recognizing these syndromes is essential, as their resolution may parallel hematologic remission [25].

4.5 Nephritic and Rapidly Progressive Glomerulonephritis (RPGN)

Nephritic presentations, marked by hematuria, hypertension, and renal impairment, are less common but clinically significant. Immune complex-mediated glomerulonephritis and cryoglobulinemic vasculitis are notable causes, particularly in lymphoplasmacytic malignancies. **Rapidly progressive glomerulonephritis (RPGN)** may occur due to crescentic transformation of glomeruli in cryoglobulinemic or immune complex disease, leading to rapid renal failure if untreated. Laboratory findings include low complement levels, elevated rheumatoid factor, and circulating cryoglobulins. Aggressive immunosuppressive and cytoreductive therapies are often required to halt progression [26].

4.6 Tubular Dysfunction and Electrolyte Abnormalities

Tubular injury in hematologic malignancies can lead to a wide range of electrolyte and acid-base disorders. **Distal renal tubular acidosis**, **Fanconi syndrome**, and **nephrogenic diabetes insipidus** have been reported, particularly in myeloma due to toxic effects of light chains on proximal tubular cells. These patients may present with hypokalemia, metabolic acidosis, glycosuria, and phosphaturia in the absence of hyperglycemia. Infiltrative and drug-induced interstitial nephritis can also disrupt tubular handling of electrolytes, leading to salt wasting or concentrating defects. Recognition of tubular dysfunction is critical, as correction of electrolyte imbalances can substantially improve outcomes and prevent cardiac or neurological complications [27].

4.7 Hypertension and Volume Overload

Hypertension in the setting of hematological malignancies can result from several mechanisms, including glomerulonephritis, chronic kidney disease, or treatment with calcineurin inhibitors. Volume overload secondary to nephrotic syndrome or renal insufficiency further exacerbates blood pressure elevation. Persistent hypertension can accelerate renal damage and increase cardiovascular risk, necessitating early pharmacological intervention with renin-angiotensin system blockers, provided serum potassium and renal function allow. Volume management with diuretics must be carefully balanced to avoid hypovolemia in patients prone to AKI [28].

4.8 Asymptomatic Laboratory Abnormalities

A subset of patients remains asymptomatic despite biochemical evidence of renal involvement. Isolated elevations in serum creatinine, mild proteinuria, or subtle urinary abnormalities may precede overt kidney disease by months. These findings warrant detailed evaluation, as they may represent early infiltration, paraprotein-related toxicity, or drug effect. Serial monitoring and timely renal biopsy when feasible can facilitate early intervention, potentially reversing reversible injury before irreversible fibrosis sets in [29].

4.9 Extrarenal and Systemic Manifestations

Renal dysfunction in hematologic malignancies rarely occurs in isolation. It is often accompanied by



systemic symptoms such as bone pain, hypercalcemia, anemia, or hepatosplenomegaly, reflecting the underlying hematologic disorder. Patients with amyloidosis may exhibit macroglossia, periorbital purpura, and cardiomyopathy, while those with cryoglobulinemia present with purpura, arthralgia, and neuropathy. Recognizing these systemic associations aids in distinguishing renal disease secondary to hematologic malignancy from coincidental primary renal pathology [30].

In essence, the clinical manifestations of renal involvement in hematological malignancies are highly variable and often nonspecific. Vigilant monitoring of renal function, urinalysis, and systemic signs in these patients is crucial for early detection and management.

5. Disease-Specific Associations

Renal disease patterns in hematological malignancies are influenced by the underlying neoplastic process, type of malignant cell, and associated circulating factors such as paraproteins and cytokines. Understanding these disease-specific associations is vital for accurate diagnosis and targeted therapy, as each hematological malignancy carries a characteristic renal signature and clinical trajectory [31].

5.1 Multiple Myeloma and Plasma Cell Dyscrasias

Multiple myeloma (MM) is the hematological malignancy most frequently associated with renal impairment, with up to 50% of patients developing renal dysfunction during their disease course. The primary renal lesions include **myeloma cast nephropathy**, **light-chain deposition disease (LCDD)**, and **amyloidosis (AL type)**. Cast nephropathy results from the precipitation of monoclonal free light chains with Tamm–Horsfall protein in distal tubules, leading to obstruction and inflammation. LCDD is characterized by nonfibrillar light-chain deposition along glomerular and tubular basement membranes, whereas amyloidosis involves fibrillar deposition of misfolded light chains within the mesangium and vessels. Clinically, MM-related kidney disease presents with proteinuria, renal failure, and sometimes nephrotic syndrome. Early reduction of serum free light chain levels using bortezomib-based regimens and supportive hydration remains the cornerstone of renal recovery [32].

Renal amyloidosis in MM presents with marked proteinuria and hypoalbuminemia, often dominating the clinical picture. The deposits exhibit apple-green birefringence under polarized light after Congo red staining and demonstrate λ or κ light-chain restriction on immunofluorescence. Renal prognosis correlates with the degree of proteinuria and response to chemotherapy. Aggressive clone-directed therapy not only improves hematologic remission but also halts progression of renal involvement [33].

5.2 Lymphomas

Renal abnormalities are common in both **Hodgkin lymphoma (HL)** and **non-Hodgkin lymphoma (NHL)**, arising from direct infiltration, paraneoplastic glomerular lesions, or treatment-related injury. Infiltration by malignant lymphoid cells can cause AKI and nephromegaly, occasionally leading to obstructive uropathy when perirenal masses compress collecting systems. Paraneoplastic glomerular diseases—such as **minimal change disease (MCD)** and **membranous nephropathy (MN)**—are particularly associated with Hodgkin lymphoma and tend to resolve following lymphoma remission. The mechanism is thought to involve T-cell cytokine dysregulation, notably IL-13, which alters podocyte permeability. In NHL, **cryoglobulinemic glomerulonephritis** and **immunotactoid glomerulopathy** are more frequent, reflecting monoclonal protein deposition. Biopsy often reveals membranoproliferative patterns with immune complex deposits [34].

Lymphoma-related interstitial nephritis and infiltration are often underdiagnosed due to nonspecific presentations. Imaging may show renal enlargement or multiple low-density lesions, while biopsy confirms lymphoid infiltration. Treatment with systemic chemotherapy frequently results in renal improvement, highlighting the reversible nature of lymphoma-associated renal dysfunction when managed promptly [35].



5.3 Leukemias

Both **acute** and **chronic leukemias** can cause renal involvement through diverse mechanisms. **Acute lymphoblastic leukemia (ALL)** and **acute myeloid leukemia (AML)** may produce renal infiltration, tumor lysis syndrome, or hyperuricemic nephropathy, leading to AKI. Direct leukemic infiltration produces interstitial expansion, tubular compression, and vascular congestion. Elevated uric acid and phosphate from high tumor turnover exacerbate injury, especially during induction chemotherapy. In **chronic lymphocytic leukemia (CLL)**, immune complex-mediated glomerulonephritis, cryoglobulinemia, and membranoproliferative patterns are frequent. CLL cells secrete monoclonal immunoglobulins or rheumatoid factors that drive these lesions. Clinically, patients present with proteinuria, hematuria, and occasionally nephrotic syndrome, which may respond to immunochemotherapy targeting B cells, such as rituximab-based regimens [36].

Rarely, **leukemic infiltration of the glomeruli** causes proliferative or membranous patterns, mimicking primary glomerulonephritis. Biopsy with immunophenotyping remains essential for differentiation. Pediatric leukemias may also manifest as renal enlargement or nephrotic-range proteinuria at presentation, highlighting the need for vigilance across all age groups [37].

5.4 Myeloproliferative Neoplasms (MPNs) and Myelodysplastic Syndromes (MDS)

Renal involvement in **myeloproliferative neoplasms (MPNs)** and **myelodysplastic syndromes (MDS)**, though less common, carries significant clinical consequences. The most frequent manifestations include **glomerulosclerosis**, **vascular changes**, and **interstitial fibrosis**, often secondary to chronic hyperviscosity, hypertension, or cytokine-driven endothelial damage. In **polycythemia vera** and **essential thrombocythemia**, hyperviscosity promotes glomerular capillary thrombosis and ischemic injury. In **primary myelofibrosis**, cytokine release and marrow fibrosis can induce secondary amyloidosis, contributing to progressive CKD. Renal biopsy in these cases may reveal segmental sclerosis, thickened capillary walls, and arteriolar hyalinosis [38].

Therapy-related injury is an additional concern. Agents such as **ruxolitinib** and **hydroxyurea**, commonly used in MPNs, have been implicated in interstitial nephritis and tubular dysfunction in rare cases. Moreover, the chronic inflammatory state inherent to MPNs may lead to secondary AA amyloidosis, particularly in longstanding disease. Control of hematologic activity and blood viscosity remains essential to mitigate renal progression [39].

5.5 Other Plasma Cell Disorders and Monoclonal Gammopathies of Renal Significance (MGRS)

Monoclonal gammopathy of renal significance (MGRS) represents a spectrum of renal disorders caused by small, often indolent B-cell or plasma cell clones that produce nephrotoxic monoclonal immunoglobulins. Though these clones do not meet criteria for overt multiple myeloma or lymphoma, their renal effects can be devastating. Lesions include **proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID)**, **C3 glomerulopathy**, and **immunotactoid glomerulopathy**. Clinically, MGRS manifests with proteinuria, hematuria, and progressive CKD. Diagnosis requires renal biopsy with immunofluorescence and mass spectrometry to identify monoclonal deposits. Management involves clone-directed therapy to suppress monoclonal production, preventing irreversible renal loss [40].

6. Diagnostic Challenges and Approaches

Diagnosing renal involvement in hematological malignancies remains a formidable task because of the overlap between malignancy-related, treatment-induced, and coincidental renal diseases. The clinical presentation is often nonspecific, necessitating a high index of suspicion and an integrated diagnostic strategy. The cornerstone of accurate diagnosis lies in the correlation of clinical features with laboratory, radiological, and histopathological findings, ideally within a multidisciplinary framework involving hematologists, nephrologists, and pathologists [41].



6.1 Laboratory Evaluation

Routine laboratory investigations are often the first clue to renal involvement. **Serum creatinine, estimated glomerular filtration rate (eGFR), and urinalysis** provide initial assessment of renal function. Detection of **proteinuria, hematuria, or casts** on urinalysis should prompt further evaluation. Quantification of protein excretion, particularly 24-hour urinary protein or spot protein–creatinine ratio, helps distinguish between glomerular and tubular proteinuria. In plasma cell dyscrasias, **serum and urine protein electrophoresis with immunofixation** is essential to detect monoclonal proteins. The **serum free light chain assay** provides sensitive measurement of κ and λ light chains, with the κ/λ ratio offering diagnostic and prognostic value [42].

Biochemical abnormalities such as **hypercalcemia, hyperuricemia, hyperphosphatemia, and hypoalbuminemia** provide indirect evidence of myeloma-related or tumor lysis–related renal injury. Additionally, markers of hemolysis (elevated LDH, low haptoglobin) and schistocytes on peripheral smear may indicate thrombotic microangiopathy secondary to chemotherapy or malignant endothelial injury. Despite their utility, routine tests often lack specificity, underscoring the need for more refined diagnostic modalities [43].

6.2 Imaging Studies

Radiologic imaging plays a complementary role in identifying structural and infiltrative renal lesions. **Ultrasonography** is a useful initial tool for assessing renal size, echogenicity, and obstruction. Infiltrative diseases such as lymphoma and leukemia may present with **bilateral nephromegaly or multiple hypoechoic nodules**. **Computed tomography (CT)** and **magnetic resonance imaging (MRI)** provide superior anatomic detail and can differentiate parenchymal infiltration from obstructive or cystic pathology. Contrast-enhanced studies, though informative, must be used cautiously due to the risk of contrast-induced nephropathy, especially in patients with impaired renal function. **Positron emission tomography (PET-CT)** is particularly valuable for detecting metabolically active lymphomatous renal infiltration and monitoring response to therapy [44].

Nuclear imaging techniques, such as **^{99m}Tc -DTPA** or **MAG3 renography**, may aid in evaluating differential renal function, particularly when nephrectomy or localized therapy is contemplated. However, imaging findings are often nonspecific and must be interpreted in conjunction with clinical and laboratory data [45].

6.3 Renal Biopsy

Renal biopsy remains the **gold standard** for diagnosing renal disease in hematological malignancies, providing definitive histopathological characterization. Light microscopy, immunofluorescence, and electron microscopy are crucial for identifying the specific pattern of injury—whether glomerular, tubular, interstitial, or vascular. Immunostaining for monoclonal immunoglobulins (κ or λ) helps confirm paraprotein-related disease, while Congo red staining identifies amyloid deposits. Flow cytometry and immunohistochemistry may detect malignant lymphoid or myeloid infiltration, distinguishing infiltration from inflammatory or drug-induced lesions [46].

However, biopsy is often **contraindicated** in patients with thrombocytopenia, coagulopathy, or advanced renal failure, limiting its use in hematologic malignancies. In such settings, **transjugular renal biopsy** offers a safer alternative, particularly in patients with severe thrombocytopenia or those requiring anticoagulation. Despite procedural challenges, histological confirmation is critical for guiding therapy, avoiding misdiagnosis, and tailoring management to the underlying pathophysiology [47].

6.4 Biomarkers and Novel Diagnostic Tools

Advances in biomarker research have opened new avenues for noninvasive diagnosis and early detection of renal injury. **Neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1**



(**KIM-1**), and **cystatin C** have emerged as sensitive markers of tubular injury, often rising before serum creatinine changes. In multiple myeloma, **serum free light chain assays** and **urinary proteomic profiling** help quantify renal risk and predict response to therapy. **Mass spectrometry-based proteomic analysis** of kidney tissue and urine can precisely identify monoclonal immunoglobulin subtypes, enhancing diagnostic accuracy in monoclonal gammopathy-related renal diseases [48].

Molecular techniques, such as **next-generation sequencing (NGS)** and **flow cytometric immunophenotyping**, facilitate detection of minimal residual disease in hematologic malignancies, correlating with renal response and relapse. Additionally, imaging biomarkers—like diffusion-weighted MRI—offer promise in differentiating inflammatory from infiltrative lesions noninvasively. While these modalities remain primarily research tools, their integration into clinical practice could revolutionize renal diagnostics in hematologic disorders [49].

6.5 Diagnostic Challenges and Differential Diagnosis

Distinguishing between malignancy-induced, treatment-induced, and coincidental renal pathology poses significant diagnostic difficulty. Drug-induced nephrotoxicity can mimic glomerulonephritis or tubular necrosis seen in malignant infiltration. Similarly, infection-related kidney injury, particularly in immunocompromised patients, can obscure interpretation. Temporal correlation between chemotherapy administration, renal dysfunction onset, and serological findings is critical for differentiation. Another diagnostic pitfall is the coexistence of **two or more pathologies**, such as paraprotein deposition with drug-induced interstitial nephritis, requiring multidisciplinary review of renal biopsy findings [50].

7. Prognostic and Therapeutic Implications

Renal involvement in hematological malignancies carries profound prognostic and therapeutic implications. The presence and severity of kidney dysfunction often dictate chemotherapy eligibility, drug dosing, transplant feasibility, and overall survival. Moreover, renal recovery following therapy is closely tied to hematologic remission, emphasizing the interdependence between the two systems. As a result, the emerging field of **onconeurology** has gained prominence, integrating nephrologic expertise into hematologic cancer management to optimize outcomes [51].

7.1 Prognostic Significance of Renal Involvement

Renal impairment at diagnosis is a **negative prognostic marker** across most hematological malignancies. In multiple myeloma, elevated serum creatinine (>2 mg/dL) or dependence on dialysis correlates with reduced overall survival and diminished response to chemotherapy. Similarly, in leukemias and lymphomas, the presence of AKI increases early mortality, limits chemotherapeutic intensity, and predisposes to treatment interruptions. Several studies have identified **serum free light chain levels**, **extent of proteinuria**, and **degree of interstitial fibrosis** on biopsy as independent predictors of renal and overall survival [52].

Chronic kidney disease resulting from irreversible tubular and glomerular damage worsens long-term outcomes, not only by reducing renal reserve but also by promoting cardiovascular morbidity. Moreover, persistent renal dysfunction increases susceptibility to infections, electrolyte disturbances, and drug toxicity. Conversely, early and aggressive management leading to renal recovery significantly improves both hematologic and overall prognoses, underscoring the need for prompt diagnosis and coordinated care [53].

7.2 Impact of Hematologic Control on Renal Outcomes

Successful hematologic control is often the **most effective renal therapy**. In plasma cell dyscrasias, reduction of monoclonal protein production using **bortezomib-, lenalidomide-, or daratumumab-based regimens** can halt ongoing renal damage and induce functional recovery. Similarly, remission of lymphoma or leukemia through chemotherapy can reverse infiltration-induced renal impairment. The close temporal relationship between hematologic and renal responses supports the concept that clone-



directed therapy remains the cornerstone of renal preservation. However, delayed intervention after significant fibrosis or tubular atrophy markedly reduces reversibility [54].

In contrast, uncontrolled hematologic disease perpetuates ongoing renal injury through persistent paraprotein deposition, cytokine release, or vascular damage. Monitoring renal parameters alongside hematologic markers is therefore critical to gauge therapeutic success and guide treatment modifications [55].

7.3 Onconeurology: An Integrated Care Model

The emergence of **onconeurology**—a multidisciplinary field dedicated to the intersection of cancer and kidney disease—has revolutionized management strategies. Onconeurologists collaborate with hematologists to tailor treatment plans that minimize nephrotoxicity while maintaining oncologic efficacy. Key aspects include **renal risk stratification**, **dose adjustment of chemotherapeutic agents**, **timely management of AKI**, and **prevention of tumor lysis syndrome**. This partnership also ensures early recognition of drug-induced nephrotoxicity, facilitating regimen modification before irreversible injury occurs [56].

Beyond clinical management, onconeurology emphasizes the importance of preventive measures such as hydration, avoidance of nephrotoxic agents, and optimization of comorbidities like hypertension and diabetes. This proactive approach improves both renal and hematologic outcomes, reducing hospitalization and mortality rates. The development of **onconeurology clinics** in tertiary centers has further enhanced integrated care delivery for these complex patients [57].

7.4 Management of Specific Renal Syndromes

Treatment of renal disease in hematological malignancies depends on the underlying mechanism. In **myeloma cast nephropathy**, prompt initiation of high-cutoff hemodialysis or plasmapheresis to remove circulating light chains, coupled with bortezomib-based chemotherapy, is recommended. **Amyloidosis** requires clone-directed therapy to suppress fibril formation, while **cryoglobulinemic glomerulonephritis** may respond to rituximab and plasma exchange. **Thrombotic microangiopathy (TMA)** secondary to chemotherapy or transplantation necessitates cessation of the offending agent and, in select cases, complement inhibition with **eculizumab**. Supportive therapy—including meticulous fluid management, correction of electrolyte disturbances, and infection prevention—is indispensable across all entities [58].

Renal replacement therapy (RRT) may be necessary in patients with severe AKI or advanced CKD. However, early intervention can sometimes obviate the need for dialysis, emphasizing the value of vigilant monitoring. When RRT is required, modalities such as **continuous renal replacement therapy (CRRT)** offer hemodynamic stability in critically ill patients. Kidney transplantation is rarely performed in active hematologic malignancy but may be considered in long-term remission [59].

7.5 Therapeutic Challenges and Drug-Induced Nephrotoxicity

Chemotherapeutic agents, immunotherapies, and targeted treatments have dramatically improved survival in hematologic malignancies but introduced new renal toxicities. **Cisplatin**, **ifosfamide**, and **methotrexate** are classical nephrotoxins, while newer drugs such as **immune checkpoint inhibitors** and **chimeric antigen receptor (CAR) T-cell therapies** may cause immune-mediated nephritis and cytokine-release-related AKI. **Tyrosine kinase inhibitors (TKIs)** like dasatinib and ponatinib have been associated with proteinuria and glomerular endothelial injury, occasionally manifesting as nephrotic syndrome. Recognizing these effects is critical for early dose modification and nephroprotection [60].

Renal monitoring protocols during therapy should include baseline assessment, serial renal function tests, and urinalysis. Preventive strategies—such as maintaining adequate hydration, avoiding concurrent nephrotoxins, and adjusting drug doses according to renal function—are essential to



minimize iatrogenic injury. In cases where nephrotoxicity develops, multidisciplinary evaluation helps differentiate between drug-induced and malignancy-related causes, guiding the decision to continue, modify, or discontinue therapy [61].

7.6 Prognostic Biomarkers and Future Therapeutic Targets

Emerging research has identified several biomarkers predictive of renal and hematologic outcomes. Persistent elevation of serum free light chains, increased urinary NGAL, and high urinary albumin excretion correlate with poor renal prognosis. Molecular profiling of renal biopsy tissue has revealed cytokine and complement activation signatures associated with treatment resistance. These insights have spurred interest in targeted therapies aimed at **complement inhibition**, **cytokine modulation**, and **fibrosis prevention**. Future therapeutic approaches may integrate these molecular strategies to protect renal function while maintaining oncologic efficacy [62].

7.7 Long-Term Outcomes and Survivorship

With improved cancer survival, long-term renal outcomes have gained increasing importance. Survivors of hematologic malignancies remain at heightened risk of CKD progression, cardiovascular disease, and recurrent malignancy. Post-treatment surveillance should include periodic renal function testing, blood pressure monitoring, and avoidance of nephrotoxic medications. Patient education regarding hydration, dietary modification, and early reporting of urinary abnormalities is crucial for long-term kidney preservation. Incorporating nephrology follow-up into cancer survivorship programs can significantly improve quality of life and reduce late renal complications [63].

Conclusion

Renal involvement in hematological malignancies represents a dynamic and multifaceted clinical challenge, reflecting the intimate interplay between the hematopoietic and renal systems. The kidney serves not only as a target of malignant and immune-mediated injury but also as a determinant of therapeutic feasibility and survival. The spectrum of renal manifestations—from subtle proteinuria to fulminant renal failure—underscores the need for vigilance and early recognition in all patients with hematologic cancers.

Understanding the **pathophysiological mechanisms**, including paraprotein toxicity, immune complex deposition, cytokine-mediated inflammation, and direct infiltration, forms the foundation for accurate diagnosis and targeted intervention. The integration of laboratory testing, imaging, and histopathology—augmented by emerging biomarkers—has improved diagnostic precision, yet significant challenges persist due to overlapping etiologies and therapy-related toxicity.

Therapeutic success hinges on timely **hematologic control**, judicious **nephroprotective strategies**, and a cohesive **onconeurology approach** that balances cancer eradication with renal preservation. As survival improves for patients with hematologic malignancies, safeguarding renal function becomes central to long-term quality of life and continued remission.

Future efforts must focus on translating scientific discoveries into clinical practice through multidisciplinary collaboration, robust clinical trials, and the implementation of precision medicine. By bridging the gap between hematology and nephrology, clinicians can transform a historically morbid complication into a manageable and, in many cases, reversible aspect of hematologic disease.

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