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Renal Failure Due to Multiple Myeloma

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Abstract

Approximately 20% of patients with multiple myeloma develop progressive kidney failure during the course of the disease. The accumulation of numerous monoclonal chains in renal parenchyma cells is usually correlated with renal failure in a patient with myeloma cancer. These light chains interact with Tamm-Horsfall protein in the distal convoluted tubule, leading to cast formation and disruption of the tubular basement membrane, resulting in acute tubular interstitial nephritis. Therefore, sufficient hydration, maintaining elevated calcium and uric acid levels, and treatment with chemotherapeutic regimens are urgent in treating such patients. Treatment should be followed with medications like thalidomide, bortezomib, and lenalidomide to prevent the severity of the disease. In addition to that, significant consideration should be given to mechanical means of treatment such as hemodialysis, kidney filters to remove the light chain blood transfusion, and many more. According to recent research and development, more efforts must be made to improve kidney function in patients with multiple myeloma and renal failure.

Keywords

Multiple Myeloma, Renal Failure, Kidney Injury, Light Chains, Treatment

1. Introduction

Myeloma is more accurately classified as a plasma cell dyscrasia or hematologic malignancy, distinct from leukemia. Although sometimes referred to as a type of leukemia, myeloma, also known as Kahler's disease, is distinct. Myeloma is a cancer of the bone marrow characterized by the presence of monoclonal protein in serum and urine. As the disease progresses, plasma cells can also be found in extramedullary locations and peripheral blood [1]. Generally, plasma cells proliferate out of the bone marrow and become widely distributed as multiple myeloma advances, leading to more severe organ damage.

Initial symptoms of multiple myeloma include pain, weakness, fatigue, weight

loss, loss of appetite, severe constipation, dizziness, and respiratory problems [2]. While there is no cure for multiple myeloma, medications can delay disease progression and, in some cases, mitigate its effects [3]. In 2020, there were an estimated 32,260 new cases of myeloma and 12,820 deaths in the United States [4]. Globally, there was a 126% increase in multiple myeloma diagnoses from 1990 to 2016, underscoring the critical need for innovative treatments [4].

Multiple myeloma can affect individuals of any race, although studies have shown that the incidence is twice as high in African American individuals, with a higher prevalence in men [5]. Approximately 1.8% of all cancers reported in the United States are multiple myeloma, accounting for 17% of total hematological malignancies [6]. Around 80% of confirmed cases exhibit chromosomal abnormalities, while the remaining patients have other genetic abnormalities [7].

The worrying situation is that the survival span is less than one year in patients with multiple myeloma who cannot recover from renal impairment. The prognosis of significant myeloma-induced renal injury is closely linked to patient survival predictors [8].

Renal failure in multiple myeloma typically occurs when the kidneys fail to filter waste products from the blood, leading to the accumulation of toxic waste and harmful substances in the bloodstream [9]. This results in a disruption of the chemical balance in the blood, causing a uremia-like condition.

2. Impact of Renal Impairment on Patient Outcomes in Multiple Myeloma

Renal impairment is a significant complication in multiple myeloma, affecting about 50% of patients at diagnosis. This condition can profoundly impact patient outcomes, including survival rates and quality of life [10].

2.1. Survival Rates

Patients with multiple myeloma and renal impairment generally have a poorer prognosis compared to those without kidney involvement. The survival span for patients who do not recover from renal impairment is typically less than one year [8]. Renal impairment at diagnosis is associated with a higher risk of early mortality, with studies indicating that up to 30% of patients with kidney injury die within the first two months of diagnosis. This high mortality rate underscores the critical need for early detection and management of renal complications in multiple myeloma.

2.2. Quality of Life

Renal impairment significantly affects the quality of life for patients with multiple myeloma. The inability of the kidneys to filter waste products from the blood leads to the accumulation of toxic substances, resulting in symptoms such as fatigue, nausea, and confusion. These symptoms can severely impact daily activities and overall well-being. Additionally, the need for treatments such as dialysis can fur-

ther reduce the quality of life, as these procedures are time-consuming and can cause additional physical and emotional stress.

2.3. Disease Progression and Organ Damage

As multiple myeloma progresses, the proliferation of plasma cells and the production of monoclonal proteins can lead to further kidney damage. This progression can result in acute kidney injury (AKI) or chronic kidney disease (CKD), both of which complicate the management of multiple myeloma and worsen patient outcomes. The increased levels of serum-free light chains in multiple myeloma patients contribute to the development of cast nephropathy, a condition where these proteins form obstructive casts in the renal tubules, leading to kidney dysfunction [11].

2.4. Management and Treatment Strategies

Effective management of renal impairment in multiple myeloma requires early intervention and tailored treatment strategies. Risk stratification for renal complications and regular monitoring of kidney function are essential for managing high-risk patients. Therapeutic approaches may include hydration, the use of medications to control calcium and uric acid levels, and the administration of chemotherapeutic agents that are less nephrotoxic. In some cases, mechanical treatments such as hemodialysis or the use of kidney filters to remove light chains may be necessary.

Renal impairment in multiple myeloma is a critical factor that influences patient survival and quality of life. Understanding the impact of kidney involvement and implementing these strategies are essential for improving outcomes in patients with this complex disease.

3. Acute Kidney Injury vs. Chronic Kidney Disease in Multiple Myeloma

Renal involvement in multiple myeloma can manifest as either acute kidney injury (AKI) or chronic kidney disease (CKD), each with distinct pathophysiological mechanisms, clinical presentations, and implications for patient management and outcomes.

3.1. Acute Kidney Injury (AKI)

Pathophysiology: AKI in multiple myeloma is often triggered by the rapid accumulation of monoclonal free light chains, leading to cast nephropathy. These light chains interact with Tamm-Horsfall protein in the distal tubules, forming obstructive casts that cause tubular damage and acute tubular interstitial nephritis [12]. Other contributing factors include hypercalcemia, dehydration, and the use of nephrotoxic agents.

Clinical Presentation: Patients with AKI typically present with a sudden decline in renal function, characterized by an increase in serum creatinine and a

decrease in urine output [13]. Symptoms may include fatigue, nausea, vomiting, and fluid overload. AKI can develop rapidly and require prompt intervention to prevent irreversible kidney damage [13].

Management: The management of AKI in multiple myeloma involves addressing the underlying causes, such as controlling hypercalcemia, ensuring adequate hydration, and discontinuing nephrotoxic medications [14]. Therapeutic plasma exchange and high-cutoff hemodialysis may be used to reduce free light chain levels [15]. Early initiation of anti-myeloma therapy is crucial to reduce the production of monoclonal proteins and mitigate renal damage [16].

3.2. Chronic Kidney Disease (CKD)

Pathophysiology: CKD in multiple myeloma results from prolonged exposure to monoclonal proteins and continuous renal damage. Chronic inflammation, fibrosis, and tubular atrophy are common features. The persistent presence of monoclonal proteins can lead to glomerular and tubular damage, resulting in a gradual decline in renal function over time [17].

Clinical Presentation: CKD is characterized by a progressive loss of kidney function, often over months to years. Patients may experience symptoms such as fatigue, anemia, bone pain, and electrolyte imbalances. CKD is typically diagnosed through persistent abnormalities in kidney function tests, such as elevated serum creatinine and reduced glomerular filtration rate (GFR) [18].

Management: The management of CKD in multiple myeloma focuses on slowing the progression of renal damage and managing complications. This includes optimizing anti-myeloma therapy, controlling blood pressure, managing anemia, and addressing bone health. Renal replacement therapy, such as dialysis, may be necessary for patients with end-stage renal disease (ESRD) [19].

3.3. Spectrum of Renal Involvement

The spectrum of renal involvement in multiple myeloma ranges from mild renal impairment to severe AKI and advanced CKD. Early detection and differentiation between AKI and CKD are essential for appropriate management and improving patient outcomes. Regular monitoring of renal function, risk stratification, and tailored therapeutic strategies are critical components of care for patients with multiple myeloma and renal involvement [20].

Generally, the kidney functioning rate is lowered to 15% of the average level. A malfunctioning kidney is seen among more than 20% of the patients who have been diagnosed with multiple myeloma. The myeloma kidney usually results in the renal failure and poses a serious risk, even accounting for death. However, the extent of kidney damage is generally balanced and flexible among 50% of the patients [21].

3.4. Risk Stratification and Monitoring Strategies

Risk stratification for renal complications in multiple myeloma involves assessing

various factors such as baseline renal function, serum-free light chain levels, hypercalcemia, genetic and chromosomal abnormalities, and comorbid conditions. Patients with pre-existing renal impairment, elevated serum-free light chains, or hypercalcemia are at higher risk for renal complications. Regular monitoring of renal function through serum creatinine, eGFR, and urine protein tests is essential for early detection of renal impairment. Imaging studies and biomarker monitoring, including cystatin C and beta-2 microglobulin, provide additional insights into renal function and disease activity [22].

Ensuring adequate hydration, managing electrolyte imbalances, and avoiding nephrotoxic medications are critical components of renal care. Early intervention at the first signs of renal impairment, such as adjusting anti-myeloma therapy and initiating treatments like plasmapheresis or hemodialysis, can prevent further damage [23]. A multidisciplinary team approach, involving hematologists, nephrologists, and other specialists, is crucial for comprehensive management of renal complications in multiple myeloma, ultimately improving patient outcomes and quality of life [24].

3.5. Renal Failure Pathogenesis in Multiple Myeloma

The pathogenesis of renal failure in multiple myeloma typically begins with the generation of defective immunoglobulin (Ig) fragments, which are generally of low molecular weight. These fragments are often produced by malignant plasma cells. The most common cause of kidney injury in patients with multiple myeloma is the accumulation of abnormal proteins produced by these plasma cells. These proteins, known as monoclonal free light chains, can bind to Tamm-Horsfall protein in the urine, forming bulky molecules that cannot be excreted through the renal tubules. This leads to the formation of obstructive casts, which have a toxic effect on the kidneys [12].

Another significant cause of kidney injury in multiple myeloma is the inflammatory reaction induced by these bulky toxic proteins. When monoclonal free light chains are reabsorbed in the convoluted tubules, they can cause programmed cell death (apoptosis) in the proximal tubule cells. This apoptosis leads to DNA disintegration, morphological changes, and an epithelial-to-mesenchymal transition. Additionally, free light chains are believed to activate several inflammatory signaling pathways, such as nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1). The activation of these pathways results in the production of pro-inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor (TNF), and macrophage chemoattractant protein 1 (MCP-1). These cytokines further enhance and activate downstream pathways, such as the mitogen-activated protein kinase (MAPK) pathway, exacerbating renal damage [12].

The historical context of free light chains (FLCs) dates back to 1845, when a 38-year-old patient in Paris exhibited bone pain and widespread inflammation. His doctor identified a distinct peptide in his urine, which was later sent to Henry Bence Jones, who gave these proteins their name. In 1963, Edelman classified these

compounds as FLCs. Under normal conditions, plasma cells produce 40% more light chains than heavy chains, facilitating the accurate assembly of intact immunoglobulins. FLCs pass through the glomerular endothelium and the basal barrier to the proximal tubule, where they are endocytosed and digested into their corresponding amino acids within tubular cells [12].

Evidence suggests that tubulointerstitial nephritis is more common in individuals with viral gammopathies [25]. In diagnosing acute tubulointerstitial nephritis (ATIN), it is essential to evaluate chronic kidney conditions related to protein chains. Histological findings in patients with lighter filament ATIN typically reveal an inflammatory tubulointerstitial process with linear stains for lambda-encoding genes and capillary extracellular matrix proteins. Vascular nephrosclerosis and mild vasculopathy are also observed and often linked to the patient's long history of diabetes. In multiple myeloma patients, kidney failure can be assessed using serum creatinine levels, which are generally greater than 1.3 mg/dL in half of the patients [20].

Additional factors contributing to kidney injury in multiple myeloma patients include elevated calcium levels due to myeloma-related bone resorption, significant fluid loss, certain nephrotoxic drugs, and diagnostic agents used during treatment [17]. Plasma cells commonly produce many light Ig fragments, which are easily filtered by the glomeruli and broken down by the renal tubules, preventing their accumulation in the kidneys. However, genetic aberrations in Ig molecules can lead to pathological inflammation and disrupted renal function. The Tamm-Horsfall protein gradually increases along the thicker ascending section of the Henle loop, interacting with filtered light Ig chains and causing toxicity in the convoluted part and epithelial cells, leading to tubular necrosis [26].

3.6. Etiology of Kidney Failure in Multiple Myeloma

Kidney failure in multiple myeloma can result from various factors associated with the disease and its progression [27]. One significant factor is the presence of tumor cells in the blood and bone marrow, which can lead to organ damage [28]. Hypercalcemia, defined as calcium levels greater than 12 mg/dL, is a common complication that can contribute to renal impairment [29]. Additionally, glomerulonephritis, characterized by a creatinine clearance of less than 40 mL/min, and elevated serum creatine kinase levels above 2 mg/dL, are indicative of kidney involvement [30].

Anemia, with hemoglobin levels below 10 g/dL, and severe bone damage are also common in multiple myeloma patients. The CRAB criteria (Calcium elevation, Renal failure, Anemia, and Bone lesions) are often used to assess the extent of organ damage [31]. Elevated levels of free light chains (FLCs) in the blood are associated with a higher risk of kidney failure. Imaging studies may reveal focal lesions in the kidneys, which can be indicative of disease progression [32].

Other contributing factors include the use of certain medications, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and contrast agents used in diagnos-

tic imaging, which can exacerbate renal impairment. Effective management of these risk factors is crucial to prevent the progression of kidney failure in patients with multiple myeloma [33].

Therapeutic management of multiple myeloma-related hyperkalemia includes basic attempts to improve fluid balance and prevent coagulation. Hypercalcemia and hyperuricemia are commonly treated to reduce additional nephrotoxins and significantly lower serum FLC levels. However, some of the patients with multiple myeloma will develop symptoms of acute kidney injury, and the efficacy of therapies or high-cutoff hemodialysis (HCO-HD) in lowering FLC levels in these patients is debatable [34].

Although the results of case series are intriguing, controlled studies have revealed little effect. Initiation of cytotoxic treatment and conditions leading to cutoff dialysis treatment can greatly reduce FLC levels. A kidney biopsy is indicated to obtain a clear diagnosis in these individuals. It is necessary if blood FLC concentrations are 5 mg/dL and fast FLC testing is not possible. A rapid cancer cure is associated with higher levels of kidney response, and individuals who achieved hemodialysis independence lived much longer than those who remained on hemodialysis [35].

In summary, acute kidney injury is a significant consequence in patients and a predictor of poor outcomes. A significant decline in blood FLC levels should begin as early as possible with radiation and chemotherapy. The attached significance and HCO-HD, in our perspective, must only be used in clinical studies at this time [36].

3.7. Pathogenesis of Multiple Cast Nephropathy Management of Renal Failure in Patients with Multiple Myeloma

Significant risk factors for kidney injury in multiple myeloma patients include increasing age, the presence of other health conditions, the severity of cancer, and the toxic effects of chemotherapy and radiation therapy [3]. Factors such as intraglomerular coagulation, altered calcium levels, phosphorus breakdown, and high lipid levels also contribute to renal disease [37]. To address fluid depletion, intravenous fluid administration is recommended. Hydration and increased urine alkalinity have been shown to promote the solubilization of light immunoglobulin G and reduce intratubular casting [38]. However, loop diuretics can cause nephron projections and are discouraged in patients with acute kidney failure due to myeloma. Intravenous fluid administration is recommended to address fluid depletion [39]. Given the lethal risk of renal failure, early administration of chemotherapeutic agents and palliative care is crucial [40].

Bisphosphonates are effective in controlling high calcium levels in the blood but can cause renal toxicity and low calcium levels, requiring close patient monitoring. Mild hypercalcemia can be treated with hydration therapy, while calcitonin and furosemide are preferred for managing high calcium levels [41] [42]. Certain drugs, including anti-inflammatory medications, aminoglycosides, ACE

inhibitors, and loop diuretics, can contribute to the development of myeloma-cast nephropathy. Restricting these drugs can reduce the risk of cast nephropathy in renal-impaired patients [27].

3.8. Treatment Options for Renal Failure in Multiple Myeloma Patients

Current treatments for kidney failure resulting from multiple myeloma include hemodialysis and combination therapies such as cyclophosphamide with dexamethasone, doxorubicin with dexamethasone, and thalidomide with dexamethasone [43]. Proteasome inhibitors like bortezomib and ixazomib have shown favorable therapeutic responses [44]. Other effective treatments include bisphosphonates, radiation, surgery, plasmapheresis, chemotherapy drugs, and stem cell transplants.

Supportive care, including hydration with intravenous fluids and treatment of hypercalcemia, is critical for patients with renal failure [29]. Recent research has highlighted promising treatment strategies involving novel antibodies such as elotuzumab (anti-SLAMF7) and daratumumab (anti-CD38), as well as histone deacetylase inhibitors like panobinostat and vorinostat [45].

Future research should focus on defining the correlation between FLC levels and kidney function at diagnosis, understanding the connection between FLC response and kidney activity, and assessing the long-term impact of renal injury [46]. Effective myeloma control is essential for increasing survival duration rather than reversing renal failure, emphasizing the need for efficacious therapy for the underlying malignancy [47]. Chronic dialysis should only be performed if the patient shows an excellent response to chemotherapy regimens [48]. Novel criteria based on eGFR measurement are recommended for patients with cancer-induced renal failure, with a high chance of significant recovery [49].

4. Therapeutics

4.1. Medications for Treating Kidney Damage in Multiple Myeloma

The combination of bortezomib and dexamethasone is currently the standard of care for multiple myeloma patients with severe kidney impairment, primarily caused by cast nephropathy. This regimen provides excellent antimyeloma activity and renal recovery. For patients resistant to bortezomib, alternatives such as thalidomide and lenalidomide are used. Additional therapeutic options include carfilzomib, pomalidomide, and monoclonal antibodies, although data on their effectiveness in patients with renal impairment (RI) are limited. In otherwise healthy individuals with renal impairment, increasing doses in conjunction with autologous stem cell transplantation should be considered. High cut-off hemodialysis filters do not appear to have any additional impact on therapy. See Table One for list of therapeutics, mechanism of action, key benefits, and adverse effects. (**Table 1**)

Table 1. Medications for treating kidney damage in multiple myeloma.

Medication	Mechanism of Action	Key Benefits	Adverse Effects	References
Bortezomib	Proteasome inhibitor	High antimyeloma activity, renal recovery	Peripheral neuropathy, thrombocytopenia	[38]
Dexamethasone	Corticosteroid, suppresses NF-κB and IL-6	Reduces M protein levels, rapid kidney response	Hyperglycemia, immunosuppression	[36]
Thalidomide	Immunomodulatory, antiangiogenic, anti-inflammatory	Effective in refractory myeloma	Neuropathy, thromboembolism	[49]
Lenalidomide	Immunomodulatory, tumoricidal action	Effective in recurrent/resistant myeloma	Venous thrombosis, neutropenia	[49]
Carfilzomib	Proteasome inhibitor	Effective in recurrent/chronic myeloma	Cardiac toxicity, renal impairment	[39]
Pomalidomide	Immunomodulatory, used with dexamethasone	Effective in relapsed/refractory myeloma	Neutropenia, thrombocytopenia	[23]

4.2. Criteria for Transplantation Eligibility

Eligibility for autologous stem cell transplantation (ASCT) in multiple myeloma patients with renal impairment depends on several factors, including disease control status and overall prognosis. The following criteria are considered:

4.2.1. Disease Control Status

- Complete Response (CR): No detectable myeloma cells in the bone marrow, normal free light chain ratio, and no evidence of disease on imaging [50]-[52].
- Complete Response (CR): Very Good Partial Response (VGPR): 90% or greater reduction in serum M protein and urine M protein level less than 100 mg/24 hours [52] [53].
- Complete Response (CR): Very Good Partial Response (VGPR): Partial Response (PR): 50% or greater reduction in serum M protein and reduction in 24-hour urinary M protein by 90% or to less than 200 mg/24 hours [52].

4.2.2. Prognosis

- Performance Status: Patients should have a good performance status (ECOG 0-2) [54].
- Renal Function: Patients with an eGFR greater than 30 mL/min are generally considered for transplantation [55].
- Comorbidities: Patients should have manageable comorbid conditions, such as controlled hypertension and diabetes [56].

Other Considerations

- Age: Generally, patients younger than 65 - 70 years are preferred candidates [57].
- Response to Initial Therapy: Patients who respond well to initial therapy are

more likely to benefit from transplantation [57].

Expanded Discussion on Transplantation

Autologous stem cell transplantation (ASCT) is a critical treatment option for eligible multiple myeloma patients, including those with renal impairment. The decision to proceed with ASCT involves a comprehensive assessment of the patient's disease control status, overall prognosis, and ability to tolerate the procedure. Patients achieving a complete response or very good partial response to initial therapy are ideal candidates for ASCT. Additionally, maintaining a good performance status and having an eGFR greater than 30 mL/min are essential criteria for eligibility.

The prognosis for patients undergoing ASCT is generally favorable, with improved survival rates and quality of life. However, careful management of comorbid conditions and close monitoring of renal function are crucial to minimize complications and ensure the best possible outcomes [39] [50].

4.3. Mechanical Means to Reduce the Severity of Kidney Failure in Patients with Multiple Myeloma

Blood exchange: Speedy elimination of toxic side light chains through blood transfer in conjunction with antimyeloma treatment may reduce permanent kidney problems by preventing additional nephropathy. A major randomized study did not find any end-to-end proof that plasma or blood transfer improves the outcome in people with multiple sclerosis and severe kidney injury. Only because the free light chain assessment was unreachable in this trial can we count out that plasma exchange may help a subset of patients. However, we feel that in some instances of the non-nephrotic syndrome, early blood exchange, forced secretion, and treatment may be beneficial [23].

Using kidney filters to remove sidelight antibody chains: Another possibility is to use hemodialysis to allow free chaining. A novel filtration barrier has been created that effectively eliminates flow of light chains has been created. A short experiment on dialysis using protein-leaking products found that it may significantly reduce the values of plasma binding to proteins. Although hopeful, such findings require validation in more extensive research [58].

Treatment with hemodialysis: Considering significant developments, the rate of death in patients with MM and symptom kidney failure within about two months after identification is more than 30%. Six Treatment response rates in individuals with MM in complex kidneys ranged from forty to Sixty percent. Moreover, excluding people who suffered during the first two years of diagnosis, the median survival of patients having MM and nonreversible final renal failure is up to two years, with 30% surviving for more than three years [59].

5. Complications of Renal Failure in Diagnosing Multiple Myeloma

Multiple myeloma patients face a 3-year survival rate, although the prognosis for

cancer patients is constantly evolving with new medications. Studies show that patients with kidney injury have a higher risk of death, reaching up to 30% within the first two months. While serum creatinine levels indicate kidney damage, defining kidney failure is complex. Calculating renal blood flow offers a more precise evaluation, and mathematical methods are widely used to measure kidney function. Assessing the therapeutic response in multiple myeloma patients with kidney disease can be challenging, especially without a clear indication of illness through serum electrophoresis [60].

In cases of oliguria or rapidly declining kidney function, urine measurements of light chains may be unreliable. Free light chains (FLCs) in the blood have been used to evaluate light chain amyloidosis and oligosecretory disease. Additionally, research has shown that cystatin C levels are higher in cancer patients, even those with typical blood creatinine levels [27].

5.1. Immunotherapy is the Treatment of Renal Failure in a Patient with Multiple Myeloma

Immunotherapies are a crucial element in cancer treatment [61]. Previous agents that cause AKI contain greater interleukin-2 and interferon [62]. Increased interleukin-2 produces cytokine production and leak capillary syndrome, resulting in prekidney azotemia. The immunotherapy drugs ipilimumab and nivolumab improve tumor death by reducing dendritic cells from the combined CTLA-4 and PD-1 receptors. Treatment modalities target gene variant alterations inside malignant tissue, successfully blocking oncogenic signals linked with tumor formation [61] [62].

In addition, these drugs have been linked to a variety of kidney problems, including AKI, proteinuria, hypertension, and electrolyte imbalances. Although very little histological information is available, BRAF inhibitor vemurafenib has been shown to cause AKI amount of the drug AKI via acute interstitial damage. This disease might be caused by blocking the MAP kinase pathway [63].

5.2. The Role of Free Light Chains (FLCs) in Renal Impairment

Cast Nephropathy: FLCs, particularly those with specific physicochemical properties, can lead to the formation of obstructive casts in the renal tubules. This occurs through their interaction with Tamm-Horsfall protein, a urinary glycoprotein. The resulting casts hinder the normal flow of urine and can cause tubular damage, leading to a condition known as cast nephropathy [64].

Direct Tubular Toxicity: FLCs can also directly damage the renal tubules through various mechanisms. These mechanisms include:

Activation of inflammatory pathways: FLCs can activate signaling pathways within renal tubular cells, leading to the production of pro-inflammatory cytokines and chemokines. This inflammatory response contributes to tubular injury and dysfunction [65].

Induction of apoptosis: FLCs can trigger programmed cell death (apoptosis) in renal tubular cells, further contributing to tubular damage and loss of function

[65].

Epithelial-to-mesenchymal transition: FLCs may promote the transformation of renal tubular epithelial cells into mesenchymal cells, a process associated with renal fibrosis and chronic kidney disease [65].

6. Discussion

Multiple myeloma is characterized by the malignant proliferation of monoclonal plasma cells, which can lead to various complications, including renal impairment, hypercalcemia, bone lesions, and anemia. These altered physiological parameters serve as diagnostic markers for multiple myeloma. Renal failure in patients with multiple myeloma is often due to the persistence of paraproteins and non-paraprotein-related complications, such as tubular nephropathy resulting from plasma cell clines generating free light chains [66].

6.1. Incorporating Latest Diagnostic Criteria

Incorporating the latest diagnostic criteria from the International Myeloma Working Group (IMWG) provides a more comprehensive overview of current diagnostic standards. The IMWG criteria include specific markers of renal damage, such as:

Serum Free Light Chain (FLC) Ratio: An abnormal FLC ratio is a key marker for diagnosing multiple myeloma-related renal impairment [67].

Renal Biopsy Findings: Histopathological examination showing cast nephropathy, tubular atrophy, and interstitial fibrosis [68].

Biomarkers of Renal Damage: Elevated levels of cystatin C and beta-2 microglobulin [69].

6.2. Renal Impairment and Plasmapheresis

Research indicates an urgency to remove light immunoglobulin chains using plasmapheresis to potentially prevent irreversible kidney failure. However, clinical studies comparing severe diuresis and chemotherapy with prolonged diuresis, chemotherapy, and plasmapheresis show only a minor advantage of plasmapheresis in terms of reversibility, with no significant difference in survival between groups [48].

6.3. Prognosis and Recovery

While the prognosis for multiple myeloma linked to kidney disorders has improved over the past two decades, there remains a 30% mortality rate, particularly from infections during the first month. Patients with typical cast nephropathy and tubular necrosis who do not have interstitial damage often recover kidney function. Kidney impairment is related to glomerular tubule shortening and inflammatory cell infiltration. The deposition of light chains along the glomerular basement membrane can lead to acute tubulointerstitial nephritis [66].

6.4. Mechanisms of Kidney Injury

The exact mechanisms of kidney injury in multiple myeloma are not fully under-

stood, but light chains are known to play a significant role. Tubular toxicity and hypercalcemia contribute to intratubular cast formation. The severity of renal disease can be better understood through kidney biopsy, which reveals the extent of tubular atrophy and tubulointerstitial fibrosis. Histopathologically, the glomerular basement layer shows immune complex deposition, leading to mesangial cell proliferation [70].

6.5. Monitoring and Management

Patients with proliferative glomerular lesions should be regularly monitored for the development of extramedullary dyscrasia. Individuals suffering from multiple myeloma-induced renal impairment require special attention, including:

Dialysis: Approximately 20% of myeloma patients undergo dialysis. Clinical physicians should consider hemodialysis for patients with severe renal impairment [27] [71].

Financial Considerations: Hemodialysis and associated patient access increase the expenses for managing multiple myeloma. Additional costs are incurred when plasma transfers are performed to maintain renal function [71].

Quality of Life: Studies on health-associated quality of life in chronic kidney illness reveal that patients' general safety and quality of life are reduced [71].

Stem Cell Transplantation: There is no difference in toxicological fatalities among patients with decreased GFRs, but those with poor GFR have higher mortality from oral disease, vomiting, and pneumonia [71].

Renal Transplantation: Kidney transplantation is not commonly considered for patients with multiple blood cancers but may be an option for those with ESRD whose myeloma is under control [71].

7. Conclusions

In conclusion, Renal failure remains a critical challenge in multiple myeloma, significantly affecting patient outcomes and survival. The accumulation of monoclonal free light chains, a hallmark of multiple myeloma, plays a central role in the pathogenesis of renal failure. These light chains, through their interaction with Tamm-Horsfall protein, lead to the formation of obstructive casts in the renal tubules, causing tubular damage and interstitial nephritis. The resulting renal impairment can manifest as acute kidney injury or chronic kidney disease, each with distinct clinical presentations and management implications.

Early detection and intervention are crucial for preventing irreversible kidney damage and improving patient outcomes. Effective management strategies include hydration, correction of electrolyte imbalances, and the use of less nephrotoxic chemotherapeutic agents. Novel therapies targeting specific molecular pathways and the use of mechanical means, such as hemodialysis and plasmapheresis, offer promising avenues for improving renal outcomes in multiple myeloma patients.

Despite significant advances in our understanding and management of multiple myeloma-related renal failure, challenges remain. Future research should focus

on identifying biomarkers for early detection, developing targeted therapies to prevent and treat renal damage, and optimizing supportive care to improve the quality of life for patients with multiple myeloma and renal complications.

Conflicts of Interest

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

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