

Analysis of chronic kidney disease on diagnosis, treatment, prognosis and related risk factors in patients with lymphoma: A mini-review

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Abstract

Currently, the field of tumor nephrology continues to evolve, and the interplay between chronic kidney disease (CKD) and lymphoma merits further investigation. The incidence of CKD among lymphoma patients is substantial, posing a significant long-term risk for CKD progression. CKD should be regarded as an independent prognostic factor for mortality in lymphoma patients. In this mini-review, we aim to extend the research direction outlined in "Diagnosis and Treatment of Secondary Nephrotic Syndrome with Rash as the Initial Symptom: A Case Report", with a focus on elucidating the correlation between CKD and lymphoma. Specifically, we will examine the onset characteristics, renal pathological changes, survival prognosis, and renal toxicity associated with various therapeutic regimens. This investigation may provide valuable insights for optimizing medical management and improving long-term outcomes in this patient population.

Keywords: Chronic kidney disease, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, Treatment progress

Introduction

CKD is characterized by structural and functional abnormalities of the kidneys resulting from a variety of etiologies. These may include pathological kidney damage with either normal or abnormal glomerular filtration rate (GFR), abnormalities in blood or urine composition, abnormal imaging findings, or an unexplained sustained decline in GFR lasting more than three months. CKD is further distinguished by its poor prognosis and prolonged disease course. According to the Global Burden of Disease Study, the global prevalence of CKD was estimated at 9.1% in 2017, with stage-specific prevalences of 5.0% for G1-G2, 3.9% for G3, and 0.2% for G4-G5. Among adults aged 20 years and older, the age-standardized prevalence of CKD was 10.4% in men and 11.8% in women. A meta-analysis of CKD prevalence in Asia indicated that China has the highest number of adult CKD patients in the region, accounting for 36.80% of all adult cases in Asia [1].

Lymphoma is a heterogeneous group of malignancies arising from B cells, T cells, or NK cells in lymph nodes and/or extranodal lymphoid tissues. Internationally, lymphomas are classified

into non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL), with approximately 85% of cases being NHL. Patients with lymphoma typically present with painless, progressive enlargement of superficial lymph nodes and may also exhibit systemic symptoms such as fever, night sweats, and pruritus. Given the widespread distribution of lymphoid tissue throughout the body, lymphoma can potentially affect any organ or tissue, including extranodal sites. There is a well-documented association between CKD and lymphoma. As early as 1995, renal involvement in patients with NHL was reported [2]. With advancements in diagnostic and therapeutic techniques, by 2000, up to 10% of NHL patients were identified as having concomitant renal impairment [3], and this proportion has been progressively increasing over subsequent years.

The Association Between CKD and Lymphoma

CKD and cancer are bidirectionally linked through various mechanisms. Cancer can lead to CKD, while CKD itself may serve as a risk factor for the development of cancer, including lymphoma [4]. The proposed mechanisms include post-renal injury due to tumor compression of the urinary tract, ischemic injury from renal vascular compression, tumor-induced autoantibody production, secretion of abnormal proteins that mediate kidney damage, direct invasion of the kidneys by tumor cells, and kidney injury secondary to tumor lysis syndrome (TLS) or radiotherapy. When tumors involve the kidneys, they often cause secondary glomerulonephritis and tubulointerstitial infiltration, leading to impaired renal function. Patients may present with symptoms such as low back pain, weight loss, hematuria, lumbar masses, or acute kidney injury (AKI) [5].

The incidence of CKD across different types of lymphoma

According to the epidemiological study by Sun *et al.* [6], among 4,638 cases of lymphoma in China, diffuse large B-cell lymphoma (DLBCL) (36.2%) was the most prevalent subtype, followed by extranodal T/NK-cell lymphoma (nasal type) (11.0%). Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) was relatively rare, accounting for only 3.7%. However, studies have indicated that in patients with lymphoma complicated by CKD, CLL/SLL is more frequently observed, followed by DLBCL and T/NK-cell lymphoma. This may suggest a higher predisposition of CLL/SLL to CKD [7].

Renal alterations in patients with CKD and concurrent lymphoma

Lymphoma-related renal pathological changes are diverse, with different types of lymphoma causing distinct renal pathologies. Renal biopsy remains an essential tool for early diagnosis. Early studies have demonstrated that minimal change nephrotic syndrome (MCNS) accounts for approximately 40% of HL-related glomerular diseases, although its overall prevalence in HL patients is only 0.4%, and it is even lower in NHL. Additionally, focal segmental glomerulosclerosis (FSGS), amyloidosis, membranous nephropathy (MN), and membranoproliferative glomerulonephritis (MPGN) have all been reported in NHL patients [8-10]. Regarding the renal pathological types in Caucasian patients, Nie *et al.* [11] collected data on 28 cases of B-cell lymphoproliferative diseases involving the kidneys over a 10-year period. Among these, seven NHL patients (all with DLBCL) exhibited pathological findings including renal amyloidosis, MN, FSGS, and IgA nephropathy. The study indicated that Ig-related nephropathies are common in B-cell lymphoma patients other than those with DLBCL and appear to significantly

impact renal survival [12]. In contrast, for Asian patients, Li *et al.* [13] retrospectively analyzed 20 lymphoma patients admitted due to CKD. Renal biopsy findings most frequently revealed MPGN, followed by crescent formation. Some patients exhibited mild glomerular lesions but severe tubulointerstitial involvement.

Prognostic considerations for patients with CKD and concurrent lymphoma

CKD may influence the prognosis of lymphoma patients. A retrospective cohort study that followed 429 lymphoma patients for three years suggested that CKD should be considered an independent risk factor for mortality in these patients [14]. However, due to the relatively short follow-up period, further research is needed to verify whether CKD accelerates lymphoma progression. Lymphoma patients also face a significant long-term risk of developing CKD, and early declines in estimated glomerular filtration rate (eGFR) may serve as an indicator of underlying lymphoma. Studies have demonstrated that lymphoma can impair renal function without direct renal infiltration, potentially leading to CKD. CKD has been observed in both patients with direct lymphoma infiltration of the kidneys and those without visible or microscopic evidence of renal involvement [15].

The prognosis of CKD following anti-lymphoma therapy

Baiyu *et al.* [16] conducted a case analysis of three patients with lymphoma and renal impairment. Among these cases, one patient's renal function improved only after anti-tumor treatment but deteriorated again prior to disease recurrence. This observation suggests that renal function may serve as a predictive marker for lymphoma recurrence. A retrospective review of 30 patients with lymphoma and CKD found that among the six patients who received anti-tumor therapy, all experienced improvement or normalization of renal function [17]. Studies have demonstrated that 70.6% of patients in the non-anti-tumor drug group achieved renal function recovery following treatment, while 72.7% of patients in the anti-tumor drug group regained renal function after discontinuation of therapy [18].

CKD and Common Anti-Lymphoma Therapeutics

Antitumor drugs exert significant effects on renal function. Close monitoring of renal function during treatment can enhance therapeutic efficacy and improve long-term patient outcomes. Novel antitumor agents have markedly extended the survival time of lymphoma patients; however, the renal toxicity associated with these drugs and its adverse impact on patient prognosis have garnered increasing attention. Traditional chemotherapy primarily induces renal injury through direct tubular toxicity, whereas newer antitumor therapies can cause a diverse range of renal injuries, including AKI, thrombotic microangiopathy (TMA), interstitial nephritis, and glomerular diseases. Given the varied pathogenic mechanisms, accurate diagnosis and tailored therapeutic approaches are essential.

The renal pathological changes induced by anti-tumor drugs are heterogeneous and frequently accompanied by AKI, with tubulointerstitial injury being the predominant feature. Molecular targeted therapies can cause a spectrum of renal injuries, including tubulointerstitial damage, TMA, and various glomerular diseases. Previous evidence suggests that the combination of immune checkpoint inhibitors and chemotherapy is associated with an increased risk of AKI [19].

Rituximab

Rituximab is a chimeric anti-CD20 monoclonal antibody used in the treatment of various B-cell NHLs. It can be administered as monotherapy or in combination with multiple regimens, including CVP and CHOP-like protocols. Yasuda *et al.* [20] evaluated 66 hemodialysis (HD) patients who received 71 different NHL chemotherapy regimens and found that serum rituximab levels in HD patients were comparable to those in patients with normal renal function. Additionally, no rituximab was detected in the dialysate, indicating that it does not exacerbate renal injury. Furthermore, rituximab can disrupt the pathogenic B-cell/CD8⁺ T-cell axis, leading to reduced T-cell cytokine production and thereby mitigating renal endothelial damage [21].

Cisplatin

Cisplatin is a platinum-based coordination compound with a square planar geometry. It has been utilized in the treatment of malignant lymphoma since 1994 [22]. However, cisplatin accumulates disproportionately in the kidneys compared to other organs, as they are the primary route of excretion. This results in a cisplatin concentration in proximal tubular epithelial cells that is approximately five times higher than in serum, leading to significant renal accumulation and subsequent cisplatin-induced nephrotoxicity [23]. Additionally, some lymphoma patients experience recurrence following cisplatin therapy. To address drug resistance and minimize adverse effects, combination therapies involving cisplatin and other agents are commonly employed in lymphoma treatment. Currently, the gemcitabine, dexamethasone, and cisplatin (GDP) regimen is an established salvage therapy for relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) [24], while R-GemOx (rituximab, gemcitabine, and oxaliplatin) is one of the most frequently used regimens for R/R DLBCL patients who are not candidates for autologous stem cell transplantation [25]. Gemcitabine, a nucleoside analog, can induce thrombotic microangiopathy and may activate the coagulation cascade, leading to direct endothelial damage and a rapid decline in renal function [26].

Chlorambucil

Chlorambucil is an anticancer agent with alkylating and immunosuppressive properties, currently utilized in the treatment of chronic lymphocytic leukemia (CLL), HL, and NHL. Studies have demonstrated that combination therapy with chlorambucil can enhance antitumor activity, resulting in a 170% increase in lymphoma mouse survival (ILS) compared to 140% for chlorambucil monotherapy. Despite its minimal renal excretion [20], mice treated with ascorbic acid in combination with chlorambucil exhibit less severe renal histopathological changes, indicating that ascorbic acid can effectively mitigate chlorambucil-induced nephrotoxicity [27]. For mucosa-associated lymphoid tissue (MALT) lymphoma, the combination of rituximab and chlorambucil has been shown to significantly improve event-free survival (EFS) and progression-free survival (PFS) in patients [28].

Bruton's tyrosine kinase

Bruton's tyrosine kinase (BTK) is a critical signaling molecule in B-cell antigen receptor pathways, playing a key role in B-cell development and activation. It is implicated in the pathogenesis of various B-cell malignancies. Ibrutinib, a first-in-class BTK inhibitor, has been approved for treating multiple B-cell malignancies

and chronic graft-versus-host disease (cGVHD). Studies have demonstrated that long-term ibrutinib use may result in degenerative tubular injury or non-oliguric AKI in the short term [29]. Some patients develop tumor lysis syndrome (TLS) following ibrutinib treatment. Discontinuation of anti-tumor therapy and initiation of HD can lead to significant improvements in renal function, uric acid levels, and phosphorus levels [30]. Although ibrutinib monotherapy or in combination with rituximab has shown promising efficacy in mantle cell lymphoma (MCL) patients, it does not prevent renal injury in patients with pre-existing renal insufficiency and may even increase the risk of unilateral ureteral obstruction and renal fibrosis following rhabdomyolysis [31].

Bendamustine

Bendamustine, a hybrid drug combining purine analog and alkylating agent properties, holds significant appeal in the treatment of newly diagnosed and relapsed lymphomas. The renal toxicity profile of bendamustine remains inconclusive. In 2011, Visani *et al.* evaluated 43 patients with refractory/relapsed lymphoma and observed no dose-limiting toxicity or grade III/IV renal toxicity during treatment [32]. A large French multicenter study highlighted early toxicities associated with bendamustine, noting that 107 patients experienced grade I-IV renal toxicity. This study suggested that higher doses (greater than 160 mg/m²) were associated with increased toxicity. However, subsequent studies have shown that significant toxicity persists even at reduced doses [33]. Therefore, further research is needed to determine the optimal dosing and scheduling of bendamustine.

Other drugs

Cytarabine, methotrexate, and ifosfamide are commonly employed in the treatment of malignant lymphoma and are frequently used in combination with other agents [34]. The precipitation of methotrexate and its metabolites within renal tubules is considered a key factor in renal function impairment [35]. Nephropathy induced by these deposits initially manifests as asymptomatic elevation of serum creatinine levels, which can progress to renal tubular necrosis and more severe renal injury. Despite preventive measures such as fluid replacement and urine alkalinization during drug administration, 2% to 12% of patients still develop AKI [36]. Ifosfamide-induced nephrotoxicity typically occurs immediately after administration but can also progress to CKD several months or years following chemotherapy, often associated with proximal tubulopathy. This toxicity is particularly prevalent in patients receiving ifosfamide-cisplatin combination therapy [37].

Conclusion

In a previous case report [38], we established the diagnosis based on the pathological findings from renal and lymph node biopsies and administered appropriate chemotherapy regimens, which led to improved patient survival outcomes. Notably, patients with CKD secondary to lymphoma are more prone to being underdiagnosed in clinical practice. Further research is warranted to investigate whether different types of renal pathology can predict specific types of lymphoma, providing potential diagnostic insights. Additionally, studying the impact of CKD on the prognosis of lymphoma patients and the effects of anti-lymphoma therapies on CKD will facilitate more effective collaborative management between nephrology and other specialties, ultimately enhancing comprehensive patient care.

Contributions

Bowen Qin wrote the manuscript, and Junhua Li revised and reviewed the manuscript. All authors were involved in the creation of the manuscript and are responsible for the content of the work. All authors contributed to the article and approved the submitted version.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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