

# Analyzing renal involvement in 100 cases of hematological malignancy

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## Abstract

**Background:** Hematological malignancies are the most common nonrenal neoplasms affecting the kidneys. The incidence and type of renal involvement in these malignancies are variable and differ according to malignancy.

**Objective:** To study the prevalence of renal involvement in hematological malignancies and to study the clinical profile of patients in various malignancies.

**Materials and Methods:** A total of 100 consecutive patients of hematological malignancies (leukemia, lymphoma, and multiple myeloma) were prospectively studied for renal involvement and clinical profile.

**Results:** There were 72 men and 28 women with mean age of  $46.85 \pm 19.23$  years. Among them, 43% patients had leukemia, 33% patients had lymphoma, and 24% patients had multiple myeloma. Renal failure was present in 37% of the total patients and one-third patients were having azotemic symptoms at presentation. Mean blood urea and serum creatinine levels were  $73.75 \pm 77.49$  and  $2.42 \pm 3.22$  mg/dl, respectively. Mean glomerular filtration rate (GFR) was  $71.29 \pm 54.92$  ml/min and 17% patients had GFR < 15 ml/min; 62.5% patients of multiple myeloma had renal failure. Four patients had acute urate nephropathy (three patients had acute leukemia and one patient had multiple myeloma). Of the total, 18% patients had hypercalcemia and 41.7% patients had myeloma. Hyperuricemia was observed in 55.5% patients. Tumor lysis syndrome was seen in three patients and all these patients were having multiple myeloma. Male sex, multiple myeloma, and hyperuricemia were significant factors contributing to renal failure ( $p < 0.05$ ).

**Conclusion:** All patients with hematological malignancies should be evaluated for renal dysfunction and all preventive measures should be used in these patients, especially when initiated on chemotherapy.

**KEY WORDS:** Hematological neoplasms, kidney, renal insufficiency, multiple myeloma, lymphoma, leukemia

## Introduction

Hematological malignancies are the most common nonrenal neoplasms affecting the kidney. They can directly infiltrate, obstruct, or can interfere with renal function by causing metabolic and immunological alterations. Therapy-induced renal involvement is another important but

preventable cause of renal failure. Although many solid and hematological malignancies may involve kidneys, clinical sequelae are usually not prominent. Lymphomas, leukemias, and multiple myeloma are most common cancers involving kidney in many fashions. The data on renal involvement in hematological malignancies from Indian subcontinent are scanty. The main objective of the present study was to evaluate renal involvement in 100 consecutive cases of hematological malignancies (leukemia, lymphoma, and multiple myeloma).

## Materials and Methods

The study was conducted at the Department of Nephrology, Oncology and Medicine in a tertiary care medical college and hospital of north India. One hundred consecutive

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patients of various hematological malignancies presenting to the hospital were included in the study. Various hematological malignancies included were Hodgkin's disease, non-Hodgkin's lymphoma, acute and chronic leukemias, and multiple myeloma. The patients included in the study were either diagnosed cases of hematological malignancies or fresh cases that were diagnosed after admission. The diagnosis was based on clinical findings, hematological findings, and bone marrow examination or other relevant investigations. The renal involvement was based on clinical parameters, urine analysis, biochemical, radiological, and if necessary histological parameters. The patients were investigated and treated on established line of treatment. After taking informed written consent, a detailed history and relevant physical examinations were carried out in each case with special emphasis on urinary symptoms and exposure to various nephrotoxic drugs. In each case, complete hemogram, routine urine examination (especially for proteinuria, hematuria, glycosuria, urine pH, and crystalluria), blood urea, serum creatinine, serum sodium, serum potassium, serum calcium, serum phosphorus, serum uric acid, serum protein, serum albumin, X-rays, and ultrasound of abdomen were carried out. Fine needle aspiration cytology, renal biopsy, and computerized tomography scan were carried out if indicated. The patients diagnosed at the time of admission were followed up for 3 months to look for any renal dysfunction. The patients were treated on established lines of treatment including dialytic support, if required, and various complications were noted.

The results were analyzed by specific statistical methods such as percentage, mean, and standard deviation using SPSS, version 12, software and appropriate tests such as Student's *t*-test or *Z* test, and *p*-value of <0.05 was considered as statistically significant.

## Results

One hundred consecutive patients of various hematological malignancies presenting to various medical specialties were included in this study. These patients were followed up over a period of 3 months and clinical renal profile was studied. There were 72 males and 28 females in this study giving a male/female ratio of 2.5:1. The mean age of the patients was  $46.8 \pm 19.2$  years with age range of 6–90 years.

### Distribution of cases according to type of malignancy

One-third of the patients were having lymphomas and slightly less than half of the patients were having leukemia (43%). Approximately one-fourth of the patients in our study had multiple myeloma. Acute leukemias were seen in 32 out of 43 patients of leukemia (74.41%). There was almost equal number of cases of acute lymphatic and acute myeloid leukemia [Table 1].

The clinical symptomatology in our study revealed that 65% patients had fever, 32% patients had symptoms suggestive of azotemia, and 23% patients had oliguria and weight

**Table 1:** Distribution of cases according to type of hematological malignancy

Group	No. of patients	Male	Female	%age of total patients
Lymphomas	33	26	7	33
NHL	30	24	6	30
Hodgkin's disease	3	2	1	3
Leukemias	43	33	10	43
ALL	16	13	3	16
AML	15	12	3	15
ABL	1	0	1	1
CML	6	4	2	6
CLL	3	3	0	3
HCL	1	1	0	1
CEL	1	0	1	1
Multiple myeloma	24	13	11	24

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; HCL, Hairy cell leukemia; CEL, chronic eosinophilic leukemia; NHL, non-Hodgkin's lymphoma

loss. Bleeding tendencies were present in 17% patients. Mean value of calculated glomerular filtration rate (GFR) (using modification of diet in renal disease equation) was  $71.29 \pm 54.92$  ml/min. Thirty-one percent of the patients had GFR of >90 ml/min, 25% patients had GFR of 60–89 ml/min, 20% patients had GFR of 30–59 ml/min, and 7% had GFR of 15–29 ml/min. Seventeen percent of the patients had GFR of less than 15 ml/min. Mean blood urea and serum creatinine were  $73.75 \pm 77.49$  and  $2.47 \pm 3.22$  mg/dl, respectively. Seven patients had serum creatinine values >8 mg/dl and required renal replacement therapy in the form of hemodialysis. Mean serum sodium was  $135.7 \pm 6.03$  meq/l and mean serum potassium value was  $4.22 \pm 0.79$  meq/l. Mean serum calcium was  $11.01 \pm 4.45$  mg/dl. Eighteen percent of the total patients had shown hypercalcemia ( $\text{Ca}^{2+} > 10.5$  mg/dl) and most of these patients had multiple myeloma. Mean value for uric acid was  $8.40 \pm 4.84$  mg/dl. Hyperuricemia (uric acid > 7.0 mg/dl) was observed in 55% patients. Out of these, 16 patients had lymphoma, 22 patients had leukemia, and 17 patients had multiple myeloma [Table 2]. Mean values for serum protein and serum albumin were  $6.96 \pm 1.29$  and  $3.12 \pm 0.62$  g/dl, respectively. Hyperproteinemia (serum protein >8.0 g/dl) was observed in 13% patients.

Proteinuria was present in approximately half of the patients (51%) and ranged from 0.3 to 1.5 g/day. None of the patients had nephrotic range proteinuria. More than half of the patients of multiple myeloma and lymphoma had proteinuria on urine examination. Approximately 40% patients with leukemia showed this abnormality. Glycosuria was present in 6% patients. The mean values of urinary pH were  $5.79 \pm 0.66$  and majority of the patients (57%) had urinary pH between 6.0 and 8.0. Fifteen percent of our patients showed evidence of pyuria (pus cells > 5/high-power field (HPF)) and only one

**Table 2:** Clinical profile of various hematological malignancies

Variable	Lymphoma N = 33	Leukemia N = 43	Multiple myeloma N = 24
Age (mean ± SD)	47.30 ± 21.30	41.79 ± 18.47	55.29 ± 8.18
Etiology	NHL – 30 (90.9%) HD – 3 (9.09%)	Acute leukemias – 32 Chronic leukemias – 10	–
Sex distribution (M/F)	26:7	33:10	13:11
Symptomatology			
Fever	20 (60.6%)	34 (79.06%)	11 (45.8%)
Weight loss	11 (33.3%)	7 (16.27%)	5 (20.8%)
Bleeding	1 (3.03%)	11 (25.5%)	5 (20.8%)
Azotemia	9 (27.2%)	10 (23.2%)	13 (54.16%)
Pallor	29 (87.8%)	43 (100%)	22 (91.6%)
Icterus	1 (3.03%)	1 (2.32%)	–
Edema	5 (15.1%)	5 (11.62%)	1 (4.16%)
LAP	16 (48.4%)	10 (23.2%)	1 (4.16%)
Mean S. creatinine (mg/dl)	1.46	2.00	4.66
Mean S. calcium (mg/dl)	9.50	9.33	10.90
Mean S. uric acid (mg/dl)	7.59	8.77	8.50
Mean GFR (MDRD)	85.45	79.58	36.95
Mean Hb (g/dl)	9.69	7.88	7.79
Mean TLC	14.45	57.42	6.65
Mean ESR (mm)	89.75	91.34	106.04
Hyponatremia	12 (36.3%)	22 (51.1%)	11 (45.83%)
Hyperkalemia	3 (9.09%)	3 (6.97%)	1 (4.16%)
Hypercalcemia	5 (15.15%)	3 (6.97%)	10 (41.66%)
Hyperuricemia	16 (48.4%)	22 (51.1%)	17 (70.8%)
Proteinuria	19 (57.5%)	17 (39.5%)	14 (58.3%)
Glycosuria	2 (6.06%)	2 (4.65%)	2 (8.33%)
M band	–	–	20 (83.3%)
Lytic lesions	–	–	9 (37.5%)

ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; S., serum; MDRD, modification of diet in renal disease.

of these had *Escherichia coli* urinary tract infection. None of the patients in our study had gross hematuria whereas microscopic hematuria ( $\geq 3$  red blood cells per HPF) was seen in 15% of the patients [Table 2].

Renal failure was present in 37% patients and maximum number of the patients had multiple myeloma (62.5%). Around one-third of the patients of lymphomas and one-fourth of patients of leukemias had renal failure at the time of presentation. Acute urate nephropathy was present in four cases out of which three cases were of acute leukemia and one case had multiple myeloma. In all these cases, uric acid levels were  $>25$  mg% and urinary uric acid/creatinine ratio was  $>1$ . Three cases had tumor lysis syndrome and all these patients had multiple myeloma. One of our patients was diagnosed to be having multiple myeloma after renal biopsy was conducted for evaluation of renal failure.

### Multiple Myeloma

Majority of the patients were elderly aged  $>50$  years with slight male preponderance. Chief presenting symptoms were azotemia followed by fever. Only few patients had bleeding tendencies at the time of presentation whereas substantial

proportion (62.5%) presented with renal failure. Three patients required renal replacement therapy in form of hemodialysis. Majority of patients were anemic and had high erythrocyte sedimentation rate [Table 2].

### Lymphoma

Although the mean age of patients with lymphomas was  $47.3 \pm 21.3$  years, 12 out of 33 patients were more than 60 years of age. There were four patients in age group of 0–20 years. Majority of the patients were male with male/female ratio of 3.7:1. Fever and pallor were most common presenting symptoms and 16 patients had peripheral lymphadenopathy at presentation. Renal failure was present in 10 out of 33 patients and mean GFR was 85.45 ml/min [Table 2].

### Leukemia

Most of the cases were of acute leukemias with fever and pallor as most common presenting features. Renal failure was present in 12 out of 43 patients and mean GFR of patients of leukemia was 79.58 ml/min. Half of the patients had hyperuricemia whereas hypercalcemia was present in very few patients [Table 2].

**Table 3:** Comparison of variable in patients with and without renal failure

Variable	With renal failure	Without renal failure	p-Value
Age (mean ± SD), years	50.2 ± 17.17	44.84 ± 20.20	0.1221
Sex distribution (male/female)	3.2:1	1.84:1	0.0405*
Etiology			
Lymphoma	10 (27.02%)	23 (36.50%)	0.169
Leukemia	12 (32.43%)	31 (49.20%)	0.100
Multiple myeloma	15 (40.54%)	9 (14.28%)	0.008*
Mean S. calcium	10.11 ± 2.32	9.56 ± 1.42	0.112
Mean S. potassium	4.31 ± 1.02	4.15 ± 0.60	0.166
Mean S. uric acid	11.66 ± 7.12	6.91 ± 2.71	0.005*
Hypercalcemia (>10.5 mg/dl)	8 (21.62%)	10 (15.87%)	0.228
Hyperuricemia (>7 mg/dl)	27 (72.97%)	28 (44.4%)	0.009*

S., serum; SD, standard deviation.

\*Significant

Though mean age of the patients with renal failure was more than patients without renal failure, it was statistically nonsignificant. The sex distribution of patients with and without renal failure was 3.2:1 and 1.84:1 ( $p < 0.05$ ). Multiple myeloma constituted the maximum number of cases with renal failure (40%) followed by leukemia (32%). Hyperuricemia was present in 73% cases having renal failure and levels of uric acid were significantly high in patients with renal failure [Table 3].

## Discussion

In this study we observed that maximum number of patients (43%) had leukemia followed by lymphoma (33%) and multiple myeloma (24%). In another study conducted on 30 patients with hematological malignancies, Khanna et al.<sup>[1]</sup> observed that there were 12 patients (40%) with multiple myeloma, 11 patients had lymphoma (36.6%), and 7 patients had leukemia (23.3%). In another study analyzing 83 patients of malignancies, lymphomas and leukemias constituted 48% and 46% patients, respectively. The patients with multiple myeloma were only 6%.<sup>[2]</sup> In our study, there were male preponderance with 72 men and 28 women as was observed in another similar study from India.<sup>[2]</sup> However, mean age in their study was 31.2 years, which is probably due to the fact that proportion of patients with multiple myeloma was only 6.2%, as compared to 24% patients in our study.

Renal failure was observed in 37% cases. Seventeen patients required renal replacement therapy at the time of presentation. Acute urate nephropathy was seen in four cases out of which three cases had acute leukemia and one had multiple myeloma. Though tumor lysis syndrome is not common in multiple myeloma, all three cases of tumor lysis in our study had multiple myeloma. The fact that only three patients developed tumor lysis syndrome in the present study is due to routine hydration and allopurinol therapy in all patients.

### Multiple myeloma

As multiple myeloma is a disease of elderly adults; in our study as well the median age of the 24 patients with multiple

myeloma was 55.3 ± 8.2 years with only 1 patient with age less than 40 years. Around two-thirds of the patients (62.5%) with multiple myeloma had renal failure. Similar observations were made by Kyle et al.<sup>[3]</sup> who found that anemia was present initially in 73% patients, hypercalcemia in 13% patients, and elevated creatinine in 48% patients. Only 2% patients in their study were younger than 40 years. In another study analyzing 26 patients of multiple myeloma with acute renal failure, the mean age of patients was 59.3 ± 7.4 years. The clinical manifestations of myeloma included anemia (100%), Bence-Jones proteinuria (80%), "M" peak in serum electrophoresis (69%), lytic bone lesions (62%), "M" peak in urine electrophoresis (54%).<sup>[4]</sup> Similar to this study, in our study as well most (83.3%) of the patients showed Mb and on electrophoresis, and 37.5% showed lytic lesions on skeletal survey. Hypercalcemia was observed in 46.7% patients and hyperuricemia was seen in 70.8% of our patients with multiple myeloma. Acute urate nephropathy was seen in one case.

Various studies have reported varying incidences of renal failure ranging from 7% to 49.5% and hypercalcemia has been found to be the most common precipitating factor for renal failure.<sup>[5-9]</sup> High incidence of renal failure in our study was probably due to usage of low threshold definition of renal failure (serum creatinine > 1.4 mg%). Studies that have reported higher figures have tended to include patients with milder degrees of azotemia without considering whether factors like dehydration had been corrected.<sup>[10-13]</sup> On applying a stricter definition of renal failure (serum creatinine > 2–2.5 mg/dl after correction of fluid deficit), however, the incidence comes down to 7%–20%.<sup>[3,11,12,14]</sup> Tubular dysfunction has been reported in patients with myeloma and Bence-Jones proteinuria. In our study, 8.3% patients with multiple myeloma had renal glycosuria.<sup>[15]</sup>

### Lymphoma

On analysis of 33 patients of lymphomas, majority of the patients were males (male/female ratio of 26:7) and were more than 50 years of age. Both Hodgkin's disease and *non-Hodgkin's lymphoma* (NHL) involve kidneys as

extranodal metastatic lymphoma and can also cause renal infiltration.<sup>[16]</sup> Renal involvement occurs more often from NHL and in our study only three of our patients had Hodgkin's disease. Hypercalcemia has been found to be a cause or contributing factor for acute kidney injury (AKI) and mean level of calcium in our study in patients with lymphoma was 9.50 mg/dl. In our study, renal failure was present in 30.3% patients. Christiansen *et al.*<sup>[17]</sup> reported incidence of AKI (defined as 50% elevation of baseline serum creatinine) in 29.39% lymphoma patients. In a recent study conducted by Khalil *et al.*,<sup>[18]</sup> the incidence of AKI was found to be 31.8%. The discrepancy between various studies could be explained by the variable criteria for inclusion adopted in various studies. Recently, Li *et al.*<sup>[19]</sup> in their analysis of 20 NHL patients with renal dysfunction and/or proteinuria found proteinuria in all the patients and impaired renal function (eGFR < 60 ml/min) in 75% patients. Microscopic hematuria was found in 15 patients (75%).

In our study, proteinuria and glycosuria were present in 57.5% and 6.06% cases, respectively. Only six patients had pyuria and two had microscopic hematuria. Lower incidence of proteinuria in our study when compared with study of Li *et al.* was probably because their study included only those patients who had renal involvement in the form of either proteinuria or AKI.

Most patients with lymphomatous infiltration have no clinical evidence of renal involvement. Urinalysis usually reveals mild proteinuria, few red and white blood cells, and occasional hyaline and granular casts.<sup>[20]</sup> Most of the patients in our study were also asymptomatic pertaining to symptoms suggestive of renal infiltration. In the largest series renal parenchyma involvement was identified in 34% of 696 autopsy cases. Of 142 patients for whom ante mortem data were available, 14% had lymphomatous infiltration diagnosed before death.<sup>[16]</sup>

### Leukemia

In our analysis, acute leukemias accounted for 32 out of 43 patients. Leukemic process can cause renal failure either due to disease itself or due to their treatment and complications.<sup>[21,22]</sup> Nephrotoxicity secondary to antibiotic treatment/chemotherapy or triggered by tumor lysis syndrome can occur, which can produce uric acid nephropathy, hypophosphatemia, or hypercalcemia with renal failure.<sup>[23]</sup> Our leukemic patients had mean serum calcium and serum uric acid levels of 9.33 and 8.77 mg/dl, respectively, and renal failure was present in 27.9% of total 43 patients. In our study also acute renal failure was multifactorial. Three patients had acute urate nephropathy with urine uric acid/creatinine ratio more than one and uric acid levels more than 25 mg%. Proteinuria, glycosuria, and microscopic hematuria were observed in approximately 40%, 8%, and 29% of the leukemia cases, respectively, which probably is suggestive of renal parenchymal involvement. Microscopic infiltration of the genitourinary tract has been considered as a cause of hematuria in these patients. There was hematuria and renal involvement at presentation in acute lymphoblastic leukemia.<sup>[24]</sup>

Tumor lysis syndrome most commonly occurs in acute lymphoid leukemias (particularly Burkitt type). Though all features of tumor lysis syndrome were present in four of our patients and none of these patients had leukemia or lymphoma, other metabolic abnormalities, such as hyperuricemia and hyperuricemia were commonly observed in our patients.

While comparing patients with and without renal failure, male sex, multiple myeloma, and hyperuricemia were found as statistically significant factors contributing to renal failure ( $p < 0.05$ ).

### Conclusion

To conclude, the results of our study show that significant number of patients with hematological malignancies have renal involvement. Multiple myeloma was most common malignancy causing renal failure. Male sex, multiple myeloma, and hyperuricemia were significant factors contributing to renal failure. Although proteinuria was observed in approximately half of the patients, none of the patients had nephrotic range proteinuria. Majority of cases of acute uratenephropathy were noticed in acute leukemia whereas all cases of tumor lysis syndrome had multiple myeloma. So, all the patients with hematological malignancies should be evaluated for renal involvement and all prophylactic measures against acute renal failure should be taken in all hematological malignancies on chemotherapy.

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