Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Clinical Study and Analysis of Kidney Disease in Patients with Hematological Malignancies

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Abstract

Background: Blood-related malignancies are the most common non-renal neoplasms affecting the kidneys. Renal involvement in patients with hematological malignancies varies according to the type of malignancy. The pathogenesis is either due to direct involvement of the kidney or related to its treatment and/or effects of chemotherapy.

Aim of the Study: This study aims to study and analyze the prevalence of kidney involvement in blood-related malignancies and to observe the clinical and laboratory profile of patients in various hematological malignancies.

Materials and Methods: A total of 93 consecutive patients of various hematological malignancies were included such as Hodgkin's disease, non-Hodgkin's lymphoma, acute and chronic leukemias, and multiple myeloma. The renal involvement was judged on analysis of patient's clinical parameters, urine analysis, biochemical, radiological, and when necessary, histological parameters. All the patients were investigated and treated on an established protocol described in literature. Patients were advised to give informed written consent followed by a detailed history taking and relevant physical examination. Patients were asked about special emphasis on urinary symptoms and usage of nephrotoxic drugs.

Observations and Results: A total of 93 consecutive patients of various hematological malignancies presenting to oncology and medicine departments were included. There were 62 (66.66%) were male and 31 (33.33%) were female with a male-to-female ratio of 2:1. The youngest patient was aged 11 years and the eldest one was 81 years with a mean age of 43.13 ± 16.2 years. Among 93 patients, 46/85 (49.46%) were diagnosed as leukemias, 27/93 (29.03%) patients had lymphomas, and 20/93 (21.50%) patients were diagnosed as multiple myelomas. Acute leukemias were seen in 27/46 (58.69%) of the patients and chronic leukemias in 19/46 (41.30%) of the patients. Forty-six patients with leukemias acute lymphatic leukemia were 7 in males (25.92%) and 3 (11.11%) in females making it a total of 10/27 (37.03%), acute myeloid leukemia was 6 (22.22%) in males and 3 (11.11%) in females with a total of 9/27 (33.33%). Acute basophilic leukemia was observed in 5 (18.51%) male patients and 3 (11.11%) female patients; total 8/27 (29.62%). Chronic myeloid leukemia was seen in 5/19 (26.31%) male and 2/19 (10.52%) female patients; 7/19 (36.84%).

Conclusions: All patients with hematological malignancies should be periodically evaluated for renal dysfunction and necessary preventive measures should be undertaken in such patients, especially when initiated on chemotherapy.

Key words: Acute leukemia, Chronic leukemia, Lymphoma, Multiple myeloma, Renal failure, Renal involvement

INTRODUCTION

Hematological malignancies are the most common non-renal neoplasms affecting the kidney.[1] These malignancies may directly infiltrate, obstruct, or can interfere with renal function by causing metabolic and immunological changes.[2] Chemotherapy-induced renal involvement is another preventable but important cause of renal failure in these patients.[3] Clinical sequelae of renal involvement are usually not prominent even though many solid and hematological malignancies involve kidneys.[4] The most common cancers involving the kidneys are lymphomas, leukemias, and multiple myeloma.[5] Compared to the world literature, the data on renal involvement in hematological malignancies from the Indian subcontinent are scanty.[6] Multiple myeloma-related renal failure is a particularly important cause of renal failure and end-stage renal disease (ESRD).[7] Nearly 20% of patients with myeloma have renal failure, and such patients have more advanced disease at diagnosis and shortened survival.[8] Although

Access this article online

www.ijss-sn.com

Month of Submission : 04-2019
Month of Peer Review : 05-2019
Month of Acceptance : 05-2019
Month of Publishing : 06-2019

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it causes only 1% of all cancers, myeloma-related ESRD accounted for 58% of all malignancy-related cases between 1997 and 2001.[9] "Tumor lysis syndrome" is described as the metabolic complication of either rapid tumor cell turnover or chemotherapy-induced tumor cell lysis. This syndrome is characterized by hyperuricemia, hyperphosphatemia, hypocalcemia, hyperkalemia, and ARF.[10,11] Tumor lysis syndrome may arise with a variety of tumors but is most commonly associated with poorly differentiated lymphomas such as Burkitt's or with leukemias, particularly acute lymphoblastic leukemia.[12] Chronic lymphocytic leukemia (CLL) can cause impaired renal function in different ways such as direct infiltration of the kidney, ureteral obstruction by lymphadenopathy, and treatment-related tumor lysis syndrome (uric acid nephropathy). Rarely, CLL has also been reported to be associated with light chain nephropathy, renal amyloidosis, membranoproliferative glomerulonephritis, granulomatous interstitial nephritis, and minimal change disease. The present study was planned to evaluate the renal involvement in 85 consecutive patients with hematological malignancies (leukemia, lymphoma, and multiple myeloma).

Type of Study

This was a prospective cross-sectional and analytical study.

Duration of Study

The study period was from September 2017 to April 2019.

Institute of Study

This study was conducted at Viswabharathi Medical College, RT Nagar, Penchikalapadu, Kurnool, Andhra Pradesh.

MATERIALS AND METHODS

In the present study, it was observed that was conducted in the departments of oncology and medicine in a tertiary care teaching medical college and hospital of Andhra Pradesh. A total of 93 consecutive patients of various hematological malignancies diagnosed in the department of oncology and medicine of the hospital were included in the study. The different hematological malignancies included were Hodgkin's disease, non-Hodgkin's lymphoma, acute and chronic leukemias, and multiple myeloma. An ethical committee clearance certificate was obtained before the commencement of the study. An ethical committee cleared consent form was used during the study. Inclusion criteria: (1) Patients of all aged with hematological malignancies were included. (2) Patients with the diagnosis of Hodgkin's disease, non-Hodgkin's lymphoma, acute and chronic leukemias, and multiple myeloma were included. (3) Patients diagnosed earlier or after the admission to the hospital were included. Exclusion criteria: (1) Patients with terminal illness were excluded. (2) Patients with immunosuppression were excluded. (3) Patients with associated malignancies were excluded. The final diagnosis was based on clinical findings, hematological findings, and bone marrow examination or other relevant investigations. The renal involvement was judged on analysis of patient's clinical parameters, urine analysis, biochemical, radiological, and when necessary, histological parameters. All the patients were investigated and treated on an established protocol described in literature. Patients were advised to give informed written consent followed by a detailed history taking and relevant physical examination. Patients were asked about special emphasis on urinary symptoms and usage of nephrotoxic drugs. All patients were subjected to a complete hemogram, routine urine examination (especially for proteinuria, hematuria, glycosuria, urinary pH, and crystalluria), blood urea, serum creatinine, serum sodium, serum potassium, serum calcium, serum phosphorus, serum uric acid, serum protein, and serum albumin. X-rays and ultrasound abdomen were carried out. Fine-needle aspiration cytology, renal biopsy, and computed tomography scan were carried out wherever indicated. All the patients diagnosed at the time of admission were followed-up for 3 months for evidence of any renal dysfunction. All the data obtained were analyzed using standard and specific statistical methods such as percentage, mean and standard deviation, and appropriate tests such as Student's *t*-test and $P < 0.05$ was considered as statistically significant.

OBSERVATIONS AND RESULTS

A total of 93 consecutive patients of various hematological malignancies presenting to oncology and medicine departments were included in the present study. These patients were followed up over a period of 3 months and clinical and renal profiles were studied. Among 93 subjects, 62 (66.66%) were male and 31 (33.33%) were female with a male-to-female ratio of 2:1. The youngest patient was aged 11 years and the eldest one was 81 years with a mean age of 43.13 ± 16.2 years. Among 93 patients, 46/85 (49.46%) were diagnosed as leukemias, 27/93 (29.03%) patients had lymphomas, and 20/93 (21.50%) patients were diagnosed as multiple myelomas. Acute leukemias were seen in 27/46 (58.69%) of the patients and chronic leukemias in 19/46 (41.30%) of the patients [Table 1].

The incidences of acute lymphatic and acute myeloid leukemia (AML) were almost equal in this study [Table 2]. Observing the distribution of cases according to the type of hematological malignancy in this study showed among the total of 46 patients with leukemia, acute lymphatic leukemia was 7 in males (25.92%) and 3 (11.11%) in females making it a total of 10/27 (37.03%), AML was 6 (22.22%) in males and 3 (11.11%) in females with a total

of 9/27 (33.33%). Acute basophilic leukemia was observed in 5 (18.51%) male patients and 3 (11.11%) female patients; total 8/27 (29.62%). Chronic myeloid leukemia was seen in 5/19 (26.31%) male and 2/19 (10.52%) female patients; 7/19 (36.84%). CLL was seen in 5/19 (26.31%) male and 1 (05.26%) female patients; total 6/19 (31.57%). Chronic hairy cell leukemia was seen in 2 (10.52%) male and 1 (05.26%) female patients; total 3/19 (15.78%). Chronic eosinophilic leukemia was seen in 2 (5.26%) male and 1 (5.26%) female patients; total 3/19 (15.78%), [Table 2].

Table 1: Distribution of patients according to the type of malignancies

Type of malignancy (%)	Number	
	Male (%)	Female (%)
Leukemias – 46 (49.46)		
Acute – 27 (58.69)	22 (81.48)	5 (18.51)
Chronic – 19 (41.30)	11 (57.89)	8 (42.10)
Lymphomas – 27 (29.03)		
NHL – 23 (85.18)	19 (82.60)	4 (17.39)
Hodgkin's – 4 (14.81)	3 (75)	1 (25)
Multiple myelomas – 20 (21.50)	14 (70)	6 (30)

NHL: Non-Hodgkin's lymphoma

Table 2: The distribution of leukemia in the study group (*n*-37)

Leukemias – 46 (%)	Male (%)	Female (%)
Acute lymphatic – 10 (37.03)	7 (33.33)	3 (11.11)
Acute myeloid leukemia – 9 (33.33)	6 (22.22)	3 (11.11)
Acute basophilic leukemia – 8 (29.62)	5 (26.31)	2 (10.52)
Chronic myeloid leukemia – 5 (26.31)	3 (11.11)	2 (10.52)
Chronic lymphocytic leukemia – 6 (31.57)	5 (26.31)	1 (05.26)
Chronic hairy cell leukemia – 3 (15.78)	2 (05.26)	1 (05.26)
Chronic eosinophilic leukemia – 3 (15.78)	2 (05.26)	1 (05.26)

Observing the presenting clinical symptomatology in the present study revealed that 63/93 (67.74%) of the patients had fever, 32/93 (34.40%) had symptoms suggestive of azotemia, and 22/93 (23.65%) had oliguria and weight loss. Bleeding tendencies were present in 17/93 (18.27%) of the patients. Mean value of calculated glomerular filtration rate (GFR) was 73.09 ± 47.52 ml/min. 30/93 (32.25%) patients had GFR of >90 ml/min, 24/93 (25.80%) 60–89 ml/min, 21/93 (22.58%) had GFR of 30–59 ml/min, and 18/93 (19.35%) had GFR of 15–29 ml/min. Mean blood urea and serum creatinine were 68.34 ± 79.10 mg/dl and 3.52 ± 2.62 mg/dl, respectively. 6/93 (6.45%) patients had serum creatinine values at >8 mg/dl and required renal replacement therapy in the form of hemodialysis. Mean serum sodium was 136.12 ± 5.93 Meq/l and mean serum potassium value was 4.13 ± 0.66 Meq/l. Mean serum calcium was 11.06 ± 3.15 mg/dl. 19/93 (20.43%) patients had values of hypercalcemia (Ca++ >10.5 mg/dl) and 14/20 (70%) of them belonged to multiple myeloma group. Mean value for uric acid was 8.14 ± 3.90 mg/dl. Hyperuricemia (uric acid >7.0 mg/dl) was observed in 51/93 (54.83%) of the patients. Out of these, 16/27 (59.25%) patients were diagnosed as lymphoma, 21/46 (27.63) had leukemia, and 17/20 (80%) patients had multiple myeloma [Table 3].

Mean value for serum protein and serum albumin was 6.16 ± 2.01 g/dl and 3.42 ± 0.91 g/dl, respectively. Hyperproteinemia (S. protein >8.0 g/dl) was observed in 15/93 (16.12%) patients. Proteinuria was present in 47/93 (50.53%) and it ranged from 0.4 to 1.7 g/day. However, none of the patients had nephrotic range of proteinuria. More than 50% of the patients with multiple

Table 3: The clinical and laboratory data of the study group (*n*-93)

Observation	Lymphoma	Leukemia	Multiple myeloma	*P* value
Age (mean±SD)	46.32±18.27	42.65±21.40	56.72±11.62	0.012
Etiology	NHL-23 HL-04	Acute leukemias-27 Chronic leukemias-19		
Sex distribution (M:F) 26:7	4.75:1 3:1	4.4:1 1.3:1	2.33:1	0.020
Weight loss 22 (23.65%)	9/93 (9.67%)	10 (10.7%)	3 (3.22%)	0.001
Symptomatology				
Fever	34 (53.96%)	19 (30.15%)	10 (15.87%)	0.031
Azotemia	18 (56.25%)	9 (28.12%)	5 (15.62%)	0.071
Oliguria	9 (40.90%)	6 (27.27%)	8 (36.36%)	0.601
Bleeding tendency	7 (41.17%)	5 (29.41%)	5 (29.41%)	0.712
Mean of calculated GFR	71.17±35.32	74.40±21.50	72.11±16.35	0.050
Mean blood urea	69.20±12.40	66.50±11.20	67.60±20.10	0.049
Mean serum creatinine	4.02±0.87	3.28±0.82	3.31±0.76	0.630
Mean serum sodium	133.45±6.25	138.80±4.12	137.91±3.43	0.044
Mean serum potassium	4.02±0.68	4.00±0.55	4.34±0.64	0.532
Mean serum calcium	10.86±1.30	11.20±1.55	10.98±0.71	0.072
Mean serum uric acid	7.98±2.10	8.30±1.05	8.10±1.00	0.810
Mean serum protein	6.02±0.78	5.80±1.02	6.31±0.99	0.570
Mean serum albumin	3.12±0.68	3.61±0.48	3.11±0.36	0.921
Mean urinary PH	5.87±1.10	5.91±0.73	6.0±0.28	0.735

GFR: Glomerular filtration rate

myeloma and lymphoma had proteinuria on urine examination. Moreover, nearly 41.86% of the patients with leukemia showed proteinuria. Glycosuria was present in 7/93 (7.52%) of the patients. The mean urinary pH among these patients was 5.59 ± 0.74 and majority of the patients 49/93 (52.68%) had urinary pH between 6.0 and 8.0 [Table 3]. 15/93 (16.12%) patients had evidence of pyuria (pus cells >5/high-power field [HPF]) and 2/93 (2.15%) of these had *Escherichia coli* urinary tract infection. No patient had hematuria, while microscopic hematuria was seen in 13/93 (13.97%) of the subjects. Renal failure was present in 26/93 (27.95%) and out of these, 16/26 (61.53%) of the patients had multiple myeloma. Around one-third of patients of lymphomas and one-fourth of patients of leukemias had renal failure at the time of presentation. Acute urate nephropathy was present in 5/93 (5.37%) patients, of which three cases were of acute leukemia and two had multiple myeloma. In all these cases, uric acid levels were >25 mg% and urinary uric acid to creatinine ratio was >1. Three cases had tumor lysis syndrome and all these patients had multiple myeloma.

DISCUSSION

The present study was conducted in a tertiary teaching hospital attached with an oncology department in Andhra Pradesh. In this study, among 93 patients, 46/85 (49.46%) were diagnosed as leukemias, 27/93 (29.03%) patients had lymphomas, and 20/93 (21.50%) patients were diagnosed as multiple myelomas. In this study, it was observed that the maximum number of patients (49.46%) had leukemia followed by lymphoma (29.03%) and multiple myeloma in (21.50%). In a similar study conducted by Khanna *et al*.[13] done on 30 patients with hematological malignancies, it was observed that there were 12 patients (40%) of multiple myeloma, 11 of lymphoma (36.6%), and 7 of leukemia (23.3%). In another study in which analysis of 83 patients with malignancies, occurrence of lymphomas and leukemias was showed as 48% and 46% of the patients, respectively.[14] However, the patients with multiple myeloma were only 6%.[14] The present study showed a male preponderance with 62 (66.66%) males and 31 (33.33%) females with a male-to-female ratio of 2:1 which was similar to the study by Banday *et al*.[14] However, the 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 21.50% in the present study. Renal failure was present in 26/93 (27.95%) and out of these, 16/26 (61.53%) of the patients had multiple myeloma. Around one-third of patients of lymphomas and one-fourth of patients of leukemias had renal failure at the time of presentation. Acute urate nephropathy was present in 5/93 (5.37%) patients, of which three cases were of acute leukemia and two had multiple myeloma. In all these cases, uric acid levels were >25 mg% and urinary uric acid to creatinine ratio was >1. Three cases had tumor lysis syndrome and all these patients had multiple myeloma. Multiple myeloma is a disease of elderly adults; as such, in our study as well, the median age of the 20 patients with multiple myeloma was 56.72 ± 11.62 years with only one patient with age <40 years. 16/26 (61.53%) patients with renal failure were found to have multiple myeloma in this study. Similar observations were made by Kyle *et al*.[15] who also found that anemia was present initially in 73% of patients, hypercalcemia in 13%, and elevated creatinine in 48% of patients. Only 2% of patients in their study were younger than 40 years.[15] Review of literature showed another study analyzing 26 patients of multiple myeloma with acute renal failur; the mean age of patients was 59.3 ± 7.4 years. The clinical manifestations of myeloma included were anemia (100%), Bence-Jones proteinuria (80%), "M" peak in serum electrophoresis (69%), lytic bone lesions (62%), and "M" peak in urine electrophoresis (54%).[16] Similarly, in this study also, 83.3% of the patients showed M band on electrophoresis and 37.5% showed lytic lesions on skeletal survey. 19/93 (20.43%) patients had values of hypercalcemia (Ca++ >10.5 mg/dl) and 14/20 (70%) of them belonged to multiple myeloma group. Mean value for uric acid was 8.14 ± 3.90 mg/dl. Hyperuricemia (uric acid >7.0 mg/dl) was observed in 51/93 (54.83%) of the patients. Out of these, 16/27 (59.25%) patients were diagnosed as lymphoma, 21/46 (27.63) had leukemia, and 17/20 (80%) patients had multiple myeloma [Table 3]. 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.[17-20] High incidence of renal failure observed in this study was probably due to the usage of low threshold definition of renal failure (S. creatinine >1.4 mg%). Studies which have reported higher figures have tended to include patients with milder degrees of azotemia without taking into consideration whether factors like dehydration had been corrected.[21-23] Tubular dysfunction has been reported in patients with myeloma and Bence Jones proteinuria. In this study, glycosuria was present in 7/93 (7.52%) of the patients. 2/20 (10%) patients with multiple myeloma in this study showed glycosuria. Analysis of 27 lymphoma patients of this study showed 23/27 (85.18%) males and 4/27 (14.81%) were female with a male-to-female ratio of 5.75:1. The mean age of this group was 46.32 ± 18.27 years. Both Hodgkin's disease and NHL lesions were found to be involving kidneys as extranodal metastatic lymphomas in 5/27 (4.62%) cases, which could have caused renal infiltration as cited by Richmond *et al*.[24] Renal involvement occurred in 3/5 (60%) cases from NHL in this study.

Hypercalcemia has been found to be a cause or contributing factor for acute kidney injury (AKI) and mean level of calcium in this study was 11.06 ± 3.15 mg/dl. 19/93 (20.43%) patients had values of hypercalcemia (Ca++ >10.5 mg/dl) and 14/20 (70%) of them belonged to multiple myeloma group. In the present study, one-third of patients of lymphomas and one-fourth of patients of leukemias had renal failure at the time of presentation. Acute urate nephropathy was present in 5/93 (5.37%) patients, of which three cases were of acute leukemia and two had multiple myeloma. In all these cases, uric acid levels were >25 mg% and urinary uric acid to creatinine ratio was >1. Christiansen *et al*.[25] reported incidence of AKI and defined as 50% elevation of baseline serum creatinine. In a study by Khalil *et al*.,[26] the incidence of AKI was found to be 31.8% and they opined that the discrepancy between various studies could be explained by the variable criteria for inclusion adopted in various studies. Recently, Li *et al*.[27] in their analysis of 20 NHL patients with renal dysfunction and/or proteinuria found proteinuria in all the patients and impaired renal function (estimated GFR <60 ml/min) in 75% of patients. No patient had hematuria in this study, while microscopic hematuria was seen in 13/93 (13.97%) of the subjects. In this study, 15/93 (16.12%) patients had evidence of pyuria (pus cells >5/HPF) and 2/93 (2.15%) of these had *E. coli* urinary tract infection. Hyperproteinemia (S. protein >8.0 g/dl) was observed in 15/93 (16.12%) patients. Proteinuria was present in 47/93 (50.53%) and it ranged from 0.4 to 1.7 g/day. However, none of the patients had nephrotic range of proteinuria. More than 50% of the patients with multiple myeloma and lymphoma had proteinuria on urine examination. Lower incidence of proteinuria in this study when compared with the study of Li *et al*.[27] was probably due to the fact that the study conducted by Liu *et al*. included only those patients who had renal involvement either in the form of 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.[28] Most of the patients in our study were also asymptomatic pertaining to symptoms suggestive of renal infiltration. In a largest series in medical literature, renal parenchyma involvement was identified in 34% of 696 autopsy cases. Out of 142 patients for whom antemortem data were available, 14% had lymphomatous infiltration diagnosed before death.[26] Acute leukemias occurred in 32/93 (34.40%) of the patients in this study accounted for 32 of 43 patients. Leukemic process can cause renal impairment[29] either due to disease itself or due to their treatment and complications. 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.[30] The leukemic patients had mean serum calcium of 11.20± 1.55 and mean serum uric acid levels of 8.30 ± 1.0 in this study and renal failure was present in 8/27 (29.6%) of them. Microscopic infiltration of the genitourinary tract has been considered as a cause of hematuria in these 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 ($P < 0.05$).

CONCLUSIONS

A significant number of patients with hematological malignancies have renal involvement. Multiple myeloma was the most common malignancy resulting in renal failure. Male sex, multiple myeloma, and hyperuricemia were significant factors contributing to renal failure. Although proteinuria was observed in around half of the patients, none of the patients had nephrotic range proteinuria. Many of the acute urate nephropathy cases were noted in acute leukemias, whereas all cases of tumor lysis syndrome had multiple myeloma. Hence, all the patients with hematological malignancies should be evaluated for renal involvement and all prophylactic measures against acute renal failure should be used in all hematological malignancies on chemotherapy.

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How to cite this article: Nikethan D. Clinical Study and Analysis of Kidney Disease in Patients with Hematological Malignancies. Int J Sci Stud 2019;7(3):66-71.

Source of Support: Nil, **Conflict of Interest:** None declared.