August 2005

Renal involvement in systemic lupus erythematosus in Pakistan

Malik Anas Rabbani
Aga Khan University

Muhammad Hammad Tahir
Aga Khan University

Bilal Karim Siddiqui
Aga Khan University

Bushra Ahmad
Aga Khan University, bushra.ahmad@aku.edu

A Shamim
Aga Khan University

See next page for additional authors

Authors
Malik Anas Rabbani, Muhammad Hammad Tahir, Bilal Karim Siddiqui, Bushra Ahmad, A Shamim, Syed Mansoor Shah, and Aasim Ahmad

Original Article

Renal Involvement in Systemic Lupus Erythematosus in Pakistan

Malik Anas Rabbani, Muhammad Hammad Tahir, Bilal Karim Siddiqui, Bushra Ahmad, A Shamim, Syed Mansoor Ahmed Shah, Aasim Ahmad
Department of Medicine, The Aga Khan University Hospital, Karachi.

Abstract

Objective: To find the prevalence of lupus nephritis, delineate its clinical, immunological and therapeutic characteristics and compare them with the data worldwide.

Patients and Methods: Between 1985 and 2001, 198 patients with SLE fulfilling the clinical and laboratory criteria of the American Rheumatism Association (ARA) admitted to the hospital were studied by means of a retrospective review of their records.

Results: Renal involvement was found in 89 (45%) patients. Biopsy showed lupus nephritis in 42 patients; there were 9 male and 33 females. Mean age at initial presentation was 27 years and mean duration of follow-up was 2 .3 years. The histological types (WHO Classification) were mainly class. 4 (n=27), class 3 (n=7) and class 5 (n=6). Immunoflourescence showed a predominantly granular pattern of IgG, IgA and C3. Renal manifestations included renal failure (50%), microscopic hematuria (67%), active urine sediment (22%), and proteinuria (74%). Proteinuria was nephrotic range in 45% patients. Treatment was with combinations of prednisolone and cyclophosphamide (n=13), prednisolone and azathioprine (n=27). 19 patients received high dose methyl prednisolone (1 gm/day for 3 days). There was no difference in mortality rate between prednisolone and cyclophosphamide and prednisolone and azathioprine treatment groups. The overall mortality rate was 17% (n=7). Mortality was higher in WHO class 4 and 5 as compared to class 2 and 3 ($p<0.001$).

Conclusion: The prevalence of lupus nephritis in our population is an intermediate between Caucasians and other Asians. Certain clinical characteristics in our patients with lupus nephritis are different as compared to various other studies. Because of limited resources for treatment in developing countries, we believe that patients with lupus nephritis should be treated with improved ancillary medical therapies and more effective immunosuppressive regimens (JPMA 55:328;2005).

Introduction

Systemic Lupus Erythematosus is no longer an exotic disease in many communities. It is becoming a frequently diagnosed condition possibly due to increased awareness of the protein manifestations and the availability of serological markers.

Renal involvement is a serious feature of systemic lupus erythematosus (SLE), occurring in 40-75% of these patients.[1,2] Despite great improvement in the management of lupus nephritis, it remains the most frequent cause of SLE-related mortality.[2]

The incidence and severity of lupus nephritis may be related to the patients' racial background[3], and studies have suggested the presence of nephropathy susceptibility genes predisposing to lupus nephritis.[1]

Lupus Nephritis remains a major cause of morbidity and mortality[4] particularly among patients of Hispanic[5] and African-American ethnicity[6] SLE patients with renal involvement are at a higher risk of dying of this disease.[7,8] Generally renal involvement is more common in Blacks[9] Indians[10] and Chinese[11], with lesser prevalence in Caucasians[11] and Arabs.[12,13]

Data on the characteristics of SLE in Pakistan seems somewhat scarce. The main purpose of this study was to review clinicolaboratory features of lupus nephritis in Pakistan and to compare it with those previously reported in other populations.

Patients and Methods

Between 1985 and 2000, 198 patients with SLE fulfilling the clinical and laboratory criteria of the American Rheumatism Association admitted to the hospital, were studied by means of a retrospective review of their records. Of these patients, 79 (40%) were admitted through outpatient clinics and rest through emergency department. Of these 198 patients, renal involvement (defined as Raised Serum Creatinine (>1.3 mg/dl), persistent proteinuria >0.5 g/day or presence of active cellular casts) was found in 89 (45%). However biopsy was not performed in all the cases, and there were only 43 cases of biopsy proven lupus nephritis. Patients with renal involvement were compared with those without it by chi square test and odds ratios were determined using 95% CI. Patients were analyzed according to their clinical symptoms and laboratory profile which included complete blood counts, serum creatinine and electrolytes, ESR, total proteins, 24 hour urinary proteins, creatinine clearance, anti nuclear factor, anti-DNA, Rheumatoid factor, serological test for syphilis, serum compliment levels, anti-ENA, chest x-ray, ultrasound kidneys and echocardiogram. Renal histological assessment

was performed by light microscopy and immunofluorescence studies. The World Health organization (WHO) classification of lupus nephritis[2], viz. class 1 normal or minimal disease, class 2 mesangial disease, class 3 focal proliferative glomerulonephritis, class 4 diffuse proliferative glomerulonephritis and class 5 membranous nephropathy, was used. The treatment was analyzed and divided into those patients who received prednisolone and azathioprine and the other group who received prednisolone and cyclophosphamide. The dose of prednisolone was initiated at 1 mg/kg of body weight and was maintained for 4-6 weeks. This was lowered gradually to a maintenance dose of 7.5-10 mg/day, once a remission was obtained. Azathioprine and cyclophosphamide were started at doses of 1 mg/kg of body weight and were gradually increased to 2 mg/kg of body weight (max.). Mean duration of treatment with AZA was 36 months where as with cyclophosphamide it was 12 months. To assess response to therapy following parameters were assessed.

* Improvement in renal function (decreased in serum creatinine, improvement in Creatinine - Clearance).
* Decrease in degree of proteinuria.
* Normalization of lupus serology (Anti ds DNA, Serum compliment levels).

For data analysis, statistical package for social science, SPSS (Release 10.0.5, standard version, 1989 - 99) was used. Univariate analysis and Fischers Exact test were used for statistical analysis.

The results were compared with various international studies. For comparing studies Chi square tests were used and Odds Ratio (OR) were calculated with 95% Confidence Intervals.

Results

There were total of 198 patients with SLE fulfilling the clinical and laboratory criteria of the American Rheumatism Association. Of these 89 (45%) had renal involvement by ARA criteria.

A comparison by Univariate analysis (Table 1) found BM suppression and serositis were significantly more in those with renal involvement. Presence of malar rash was significantly less in this group. Although males had higher odds of having renal involvement, but it failed to reach a statistical significance. Mortality Rate was higher in those with renal involvement.

Forty two patients had biopsy proven lupus nephritis. Of these, 9 were male and 33 were females. Mean age at initial presentation was 27 years and mean duration of follow-up was 2.3 years.

The commonest presenting symptoms were fever, musculoskeletal and mucous membrane involvement. Fever was present in 16 (38%) arthritis in 12 (28%) and oral ulcers in 12% patients. Skin involvement occurred in 27 patients (76%) and included malar rash (26%), photosensitivity (4%), discoid rash (17%) and alopecia (17%).

Other manifestations included central nervous system (CNS) involvement in 9 patients (n=21%), seen as seizures in 3, psychosis in 4 and CNS infarctions in 2 patients. 48% of the patients were hypertensive at the time of presentations.

Infections occurred in 48% patients (n=20). These consisted of respiratory tract infections in 14% patients, urinary tract infections in 26%, CNS infections 2%, skin infections or cellulitis 14%, thrush in 5% and septicemia with DIC (disseminated intravascular coagulation) in 12%. The commonest pathogens were E.coli (17%), Klebsiella (9%),

Table 1. Univariant analysis between those with renal involvement and those without it.

	Renal involvement (%)	No Renal involvement (%)	P value	OR (95% CI)
Female	42.5	67.5	0.065	0.44 (0.18-1.07)
Male	62.5	37.5		
No Bone marrow suppression	42.7	57.3	0.017	0.224 (0.06-0.84)
Bone Marrow suppression	76.9	23.1		
Malar rash	33	67	0.030	0.50 (0.266-0.941)
No malar Rash	50	50		
Serositis	59	41	0.033	2.08 (1.05-4.12)
No Serositis	40.9	50.1		
≤3 hospitalizations	41	59	0.013	0.38 (0.17-0.83)
>3 hospitalizations	65	35		
Dead	65	35	0.010	2.75 (1.24-6.07)
Alive	40.5	59.5		

Pseudomonas (7%), Staphylococcus areus (5%), and Candida albicans (3%).

Lymphoreticular involvement occurred in 14% patients and consisted of lymphadenopathy in 3%, hepatosplenomegaly in 11%. Cardiac involvement was encountered in 8% patients and consisted of pericarditis in 5%, myocarditis in 3% and 19% had pleural effusion.

Of the hematological involvement, 69% had anemia (Hb<11 gm/dl), 21% patients developed leukopenia (WBC<4x10^9/L), 21% thrombocytopenia (platelets <150x10^9/L), 48% lymphopenia and 12% developed pancytopenia. Hemolytic anemia was present in 3% patients. Deep vein thrombosis, pulmonary embolism and abortions did not occur in any patient. Two patients had family history of systemic lupus erythematosus.

Laboratory Data

Renal Function and Investigations

Fifty percent patients had elevated serum creatinine (normal <1.3 mg/dl). Mean serum creatinine at presentation was 2.48mg/dl (range 0.4-16.60 mg/dl). Mean serum Cr in Class 4 was 2.49mg/dl (St. Dev ±3.33), in Class 5, 1.5mg/dl (St Dev. ±1.53) and Class 3, 2.7mg/dl (St. Dev. ±4.32).

Seventy percent patients had proteinuria at presentation (Table 3). Mean protein excretion in urine at presentation was 3.6 grams/24 hours (range 11-12800 mg/day). Of these, 45% had nephrotic range proteinuria, 67% patients microscopic hematuria and 22% active urine sediments at presentation.

Renal Histology

The indications for renal biopsy were proteinuria (+1 to +4 on albustix testing) or active urinary sediment (red blood cell, granular cast, broad cast in a urine specimen) and renal failure (Serum Cr. >1.3 mg/dl). There were 27 patients with WHO class 4, 7 with class 3, 6 with class 5 and 3 patients with class 2.

Immunofluorescence studies

Sixty percent patients were positive for IgG, 20% for IgA, 15% for IgM and 20% for C3.

Treatment

Various treatment combinations used were, prednisolone and cyclophosphamide (n=13), prednisolone and azathioprine (n=27) whereas 19 patients received methyl prednisolone. Cyclosporine and chlorambucil were used in one patient each.

Table 2. Univariant analysis for risk factors of mortality in biopsy proven Lupus Nephritis.

	Dead (%)	Alive (%)	P value	OR (95% CI)
Infection	35	65	0.003	2.69 (1.75-4.14)
None	0	100		
Neurological involvement	43	57	0.07	5.8 (0.94-36.0)
None	6	94		
Alopecia	56	44	0.009	0.07 (0.01-0.47)
None	08	92		

(Fischers Exact test used in all, because of small n).

Follow-up

Forty percent patients were lost to follow-up. In-hospital mortality was 17% in patients who did not undergo renal biopsy (16% in biopsy group). The main cause of death

Table 3. Differences in Autoantibodies, Complement Levels and Renal Function abnormalities between various countries and Pakistan.

	Pakistan n= 43, n (%)	Lebanon[14] n=50, n (%)	China[11] n=180, n (%)	UAE[12] n=21	Belgrade[8] n=58	Thailand[23] n=568
ANA	26 (79)	45 (90)		16 (94)	55 (95)	
Anti dsDNA	25 (74)	40 (80)	126 (69)	21 (100)	42 (72.2)	
Low C3	36 (86)	30 (60)*	136 (74)	12 (60)		
Raised Serum Creatinine	21 (50)	16 (32)			(25)	(46)
Proteinuria	31 (74)	46 (92)				
Nephrotic range	23 (55)	13 (26)	61(34)			(41.3)
Non-Nephrotic range	08 (19)	33 (66)				
Active Urinary Sediment	37 (88)	23 (46)				

was infections (86%) and CNS involvement (14%) (Table 2). The infections were mainly of urinary tract and chest. When cyclophosphamide and azathioprine groups were compared at the end of 2 years follow-up, no difference was noted in the mortality rate. Analysis of data further revealed that mortality rate was higher in WHO class 4 and 5 (18%) as compared to class 2 and 3 (11%) ($p<0.001$).

It is difficult to evaluate Renal-Survival considering the significant number of patients lost to follow-up. Of those the who continued to come, only two patients developed ESRD requiring dialysis. Both of these patients received cyclophosphamide.

As far as the prognostic factors are concerned, renal involvement was the single most important predictor of poor outcome. However despite this there was no difference in mortality in those who presented with higher serum Cr values as compared to those with relatively lower serum Cr values.

Discussion

Lupus Nephritis as an entity has not been studied before in Pakistan. Literature on SLE in Pakistan is scarce. Cutaneous manifestations of lupus in Pakistani patients have been presented by Rabbani et al[15] and another study by Suleman et al[16] discussed the relevance of classification set forth by American Rheumatology Association to local lupus patients. We believe that under reporting of lupus in Pakistan has given ground to the false belief that SLE is not a common disease in Pakistan. The true frequency of SLE, however, can only be obtained by conducting a community-based study.

It is known that lupus nephritis has a higher prevalence in Indians[10], Chinese[11] and Blacks[9] than Caucasians.[11]

Paradoxically, our study showed a lower prevalence of renal involvement (45%) as compared to the Indians (73%)[10], Blacks (78%)[19], Chinese (54%)[11] and Arabs[12] (54%). This suggests that the prevalence of renal involvement in our population is intermediate between Asian and Caucasians (39%).

We found lower frequency of malar rash in patients with lupus nephritis. In contrast, Anay J M et al[17], in a cross-sectional multicenter study in Colombia observed that patients who developed nephritis had a higher frequency of oral ulcers (41% vs. 21%, OR = 3.1, 95% CI: 1.3-7.5 p = 0.01) and malar rash (77% vs. 45%, OR = 4.4, 95% CI: 1.8-10.8, $p<0.001$). Our study also shows that patients with renal involvement are high risk group in SLE as there were significantly more deaths in them which is consistent with many other studies.[7-8] The overall mortality rate in our study was 17% which is higher than other studies worldwide.[12] We believe that actual mortality rate is much higher in our patients than what is reflected by our study as many of the patients are lost to follow-up as suggested by mean follow up period of less than 3 years.

The male to female ratio in those with biopsy proven SLE was lower than Arabs[12], Americans and Orientals.[23] Mean age, however was consistent with other studies[12], The main histological types were WHO class 3 (17%), class 4 (64%) and class 5 (14%). This study also revealed that we had the highest prevalence of WHO histological class 4 as compared to Indians, Orientals, Blacks, Africans, Arabs, Americans and Europeans.[12] A higher prevalence of Grade III lesion is seen in the Chinese population[11] which may suggest that there is some genetic component which determines the type of renal lesion. However higher prevalence of Class 3 and 4 may also be due to the fact that renal biopsy was done in selective cases.

Univariate analysis by Fischer's Exact test showed higher mortality in those with alopecia and infections. All those who died had underlying infections. A Chinese study[11] also found that most of their deaths were due to infections. It seems that increased risk of acquiring infections was associated with aggressive immunosuppression therapy used in class 4 and 5 that lead to bone marrow-suppression and overwhelming sepsis. It is important to note that all patients who developed marrow suppression due to immunosuppressive agents invariably developed infections. Bone-marrow suppression secondary to immunosuppression was defined as leukopenia or thrombocytopenia or both, warranting reduction of dose of the immunosuppressive drug. In all patients the status of leukopenia and thrombocytopenia had been confirmed by repeated complete blood counts. The cytotoxicity of immunosuppressive drugs was confirmed by clearly improving blood pictures following reduction of the respective doses of CYC and AZA.

Immunosuppressive regimens, at present, mainly rely on western guidelines that were derived from studies conducted in western populations. Unfortunately, no such study exists for South Asian population, which is home to over one billion people, different in both genetics and environment from west. Locally derived thresholds markedly differ from western figures.[24] This may warrant re-adjustment of current local immunosuppressive regimens that are at present based largely on western guidelines.

Studies have shown that auto antibodies may play a role in pathogenesis of lupus nephritis. High-titer antibodies to dsDNA, for example, have been identified in lupus nephritis and their levels tend to rise and fall with the disease.[13] This widely recognized correlation has been reported in several populations of lupus patients including Caucasians[18], Afro-Caribbeans[19] and Asians.[10] Studies have shown that DNA-anti dsDNA antibody complexes indeed

participate in the pathogenesis of lupus nephritis. When autoantibody profile in biopsy proven lupus nephritis was compared to various studies, ANA was found to be lower[12] but there was no difference in the prevalence of anti dsDNA.[12] However we could not find any correlation between anti dsDNA titers with nephritis.

Serum complement abnormalities tend to parallel the activity of lupus nephritis.[19] Persistent depression of C3 complement has been associated with progression of kidney disease in some, but not all, groups of patients.[19] Declining C3 or C4 are predictors of exacerbations of lupus nephritis. Occurrence of high-grade proteinuria has not emerged as a consistent predictor of renal failure in patients with lupus nephritis.[20] In our patients there was a higher incidence of C3 hypocomplementenemia and nephrotic range protein as compared to various studies worldwide.[12]

In our study there was no difference in the 2 modality groups (prednisolone/azathioprine and prednisolone/cyclophosphamide). Intravenous pulse cyclophosphamide is shown to be superior in terms of efficacy and survival in many studies.[21,22] However our experience in local population has shown that it is associated with high rates of mortality secondary to severe bone marrow suppression and serious infections.

Conclusion

This is the first study on lupus nephritis in Pakistan. We have found that the prevalence of lupus nephritis in our population is an intermediate between Caucasians and other Asians. It was seen that certain clinical characteristics in our patients with lupus nephritis have different prevalences as compared to various other studies.

In conclusion lupus nephritis in Pakistan is associated with high rate of morbidity and mortality. The WHO classification of lupus nephritis as judged by our experience does give some idea about prognosis. Serious infections associated with aggressive immunosuppression used in class 4 and 5 are the main cause of mortality. We therefore recommend that our local lupus patients not only need improved ancillary medical therapies and readjusted immunosuppression regimens according to local thresholds but also closer monitoring and follow-up, particularly seeking and treating infections vigorously.

References

1. Tsao BP. Genetic susceptibility to lupus nephritis. Lupus 1998;7:585-90.
2. Golbus J, McCune WJ. Lupus nephritis: classification, prognosis, immunopathogenesis, and treatment. Rheum Dis Clin N Am 1994;20:213-42.
3. Hochberg MC Boyd RE, Ahearn JM, Arnett FC, Bias WB, Provost TT, Stevens MB. Systemic lupus erythematosus: a review of clinico-laboratory features and immunogenetic markers in 150 patients with emphasis on demographic subsets. Medicine (Baltimore) 1985;64:285-95.
4. Esdaile JM, Abrahamowicz M, MacKenzie T, Hayslett JP, Kashgarian M. The time-dependence of long-term prediction in lupus nephritis. Arthritis Rheum 1994;37:359-68.
5. Pistiner M, Wallace DJ, Nessim S, Metzger AL, Klinenberg JR. Lupus erythematosus in the 1980s: a survey of 570 patients. Sem Arthritis Rheum 1991;21:55-64.
6. Wallace DJ, Podell TE, Weiner JM, Cox MB, Klinenberg JR, Forouzesh S, et al. Lupus nephritis. Experience with 230 patients in a private practice from 1950 to 1980. Am J Med 1982;72:209-20.
7. Alarcon GS, McGwin G Jr, Bastian HM, Roseman J, Lisse J, Fessler BJ, et al. Systemic lupus erythematosus in three ethnic groups VII: Predictors of early mortality in the LUMINA cohort. Arthritis Rheum 2001;45:191-202.
8. Austin HA 3rd, Boumpas DT, Vaughan EM, Balow JE. High-risk features of lupus nephritis: importance of race and clinical and histological factors in 166 patients. Nephrol Dial Transp 1995;10:1620-8.
9. Hernandez-Cruz B, Tapia N, Villa-Romero AR, Reyes E, Cardiel MH. Risk factors associated with mortality in systemic lupus erythematosus. A case-control study in a tertiary care center in Mexico City. Clin Exp Rheumatol 2001;19:395-401.
10. Abu-Shakra M, Urowitz MB, Gladman DD, Gough J. Mortality studies in systemic lupus erythematosus. Results from a single center. II. Predictor variables for mortality. J Rheumatol 1995;22:1265-70.
11. Nossent JC. Systemic lupus erythematosus on the Caribbean Island of Curacao: An epidemiological investigation. Ann Rheum Dis 1992;51:1197-201.
12. Malaviya AN, Chandrasekaran AN, Kuamr A, Sharma PN. Systemic lupus erythematosus in India. Lupus 1997;6:690-700.
13. Julian T, Uramoto, W. Michael O' Fallon. A Comparative Study of the Clinical Manifestations of Systemic Lupus Erythematosus in Caucasians in Rochester, Minnesota, and Chinese in Singapore, From 1980 to 1992. Arthritis Care & Research 2001;45:494-500.
14. Uthman IW, Muffarij AA, Mudawar WA, Nasr FW, A-FM Masri Lupus nephritis in Lebanon, Lupus 2001;10:378-81.
15. Rabbani MA, Shah SMA, Ahmad A. Cutaneous manifestations of SLE in Pakistan. J Pak Med Assoc 2003;53:539-41.
16. Suliaman K, Sohail KS, Raza F, Siddiqur A. Clinacal spectrum of SLE at Aga Khan University Hospital. J Pak Med Assoc. 2000;50:364-7.
17. Al-Attia HM, Al Ahmed YH, Chandani AU. Serological markers in Arabs with lupus nephritis. Lupus 1998;7:198-201.
18. Neumann K , Wallace DJ, Azen C, Nessim C, Fichman M, Metzger AL, et al. Lupus in the 1980s: III. Influence of clinical variables, biopsy, and treatment on the outcome in 150 patients with lupus nephritis seen at a single center. Semin Arthritis Rheum 1995;25:47-55.
19. Swaak AJ, Huysen V, Nossent JC, Smeenk RJ. Antinuclear antibody profiles in relation to speciFIc disease manifestations of systemic lupus erythematosus. Clin Rheumatol 1990;9:82-94.
20. Villarreal GM, Drenkard C, Villa AR, Slor H, Shafrir S, Bakimer R, et al. Prevalence of 13 autoantibodies and 16/6 and related pathogenic idiotypes in 465 patients with systemic lupus erythematosus and their relationship with disease activity. Lupus 1997;6:425-35.
21. Laitman RS, Glicklich D, Sablay LB, Grayzel AI, Barland P, Bank N. Effect of long-term normalization of serum complement levels on the course of lupus nephritis. Am J Med 1989;87:132-8.
22. Illei GG, Austin HA, Crane M, Collins L, Gourley MF, Yarboro CH, et al. Combination therapy with pulse cyclophosphamide, plus pulse methyl prednisolone improves long term renal outcome. Without adding adding toxicity in patients with lupus nephritis. Ann Intern Med. 2001;135:248-57.
23. Chan AY, Hooi LS. Outcome of 85 lupus nephritis patients treated with intravenous cyclophosphamide: A single center 10 years experience. Med J Malaysia 2000;55:14-20.
24. Ali SS, Rabbani MA, SSM Moinuddin S Virani, Farooque F, Salam A, Ahmad A. Maximum tolerable dose of cyclophosphamide and azathioprine in Pakistani patients with primary renal disease. J Pak Med Assoc 2004;54:39-42.