

Late Onset Lupus Nephritis: Analysis of Clinical Manifestations and Renal Pathological Features in Siriraj Hospital

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Background: Lupus nephritis (LN) is uncommon after the age of 50 years and studies of elderly patients with LN are rare. The authors conducted the current study to determine the clinical manifestations, pathological features and prognosis of 30 Thai patients with late onset LN in Siriraj hospital in Bangkok from 1989 to 2006.

Material and Method: Thirty LN patients with a disease onset beyond the age of 50 years from 1989 to 2006 were enrolled in this retrospective study. All of them received renal biopsy. The histological classifications were categorized according to 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification.

Results: Clinical and pathologic records were collected from 30 patients (23 female and 7 men) who were followed-up for a mean period of 25.8 months (range, 6 to 96 months). The mean age was 56.6 ± 4 years. Hypertension was diagnosed in 66.7% of patients and 41.3% had serum creatinine greater than 1.5 mg/dL. Nephrotic-range proteinuria was found in 63.3% of patients and creatinine clearance less than 50 ml/min was found in 70%. Of the 30 patients, the most common renal histologic finding was diffuse proliferative glomerulonephritis (63.3%). The overall probability of patient survival was 94.1% at 12 months, 68.6% at 36 months and 34.3% at 60 months. During the follow-up period (25.8 months; range, 6 to 96 months), 4 patients died. Infection was the leading cause of death (75%).

Conclusion: Lupus nephritis in the elderly patients is not uncommon. Prompt diagnosis should be made for appropriate management and optimal outcome.

Keywords: Late onset lupus nephritis, Elderly, Nephrotic-range proteinuria, Renal pathology

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Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease predominantly affecting women, with a high incidence during the childbearing age, a decline after menopause and a frequent exacerbation during pregnancy, suggesting that estrogens act as a precipitating factor. However, SLE can also be observed in children and in the elderly. Age at onset has been recognized as modifying effect on the clinical manifestations of SLE, so the elderly or late onset patients may constitute a specific subgroup

of SLE⁽¹⁻⁷⁾. SLE is characterized by variable clinical and laboratory manifestations. Renal involvement is common in SLE. Abnormal urinalysis with or without an elevated plasma creatinine concentration is present in a large proportion of patients at the time of diagnosis and may eventually develop in up to 75% of the cases^(8,9). Lupus nephritis has been identified as an important predictor of poor outcome in virtually all studies of SLE patients⁽¹⁰⁾. Late onset lupus nephritis patients seem to have a more insidious onset, be less likely to have major organ involvement and have less degree of disease activity^(2,3). However, studies of late onset lupus nephritis were rare and histological findings were seldom reported in the literature. To evaluate the prevalence, clinical manifestations, renal histological

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features and prognosis of Thai patients with late onset lupus nephritis in Siriraj Hospital, the authors thought it would be beneficial to make prompt diagnosis which would finally lead to proper management and excellent outcomes.

Material and Method

Study design

Data collection was achieved by retrospective chart review of the patients in Siriraj Hospital. Late-onset lupus nephritis was defined as patients who had diagnosis of lupus nephritis at or over 50 years old. From October 1989 to August 2006, thirty patients were identified as having late-onset LN and enrolled in the present study. The following items were recorded: age, sex, blood pressure, renal and extrarenal manifestations, complete blood count (CBC), blood chemistry including serum creatinine, electrolytes, albumin, cholesterol, triglyceride, urinalysis, 24 hour urine protein excretion and creatinine clearance, antinuclear antibody (ANA), anti-double strand DNA (anti-dsDNA). Renal histological classification of renal tissues were determined according to 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) that divided them into 6 classes⁽¹¹⁾:

Class I: Minimal mesangial lupus nephritis

Class II: Mesangial proliferative glomerulonephritis

Class III: Focal lupus nephritis

Class IV: Diffuse lupus nephritis

Class V: Membranous lupus nephritis

Class VI: Advanced sclerosis lupus nephritis

Statistical analysis

Descriptive statistics for continuous variables were expressed as mean \pm SD (standard deviation). Categorical variables were expressed as proportions (percentage). Survival was described with the product-limit method.

Results

From October 1989 to August 2006, 30 patients were included in the present study. The female to male ratio was 3.29:1 (female 23 and male 7). The mean age was 56.6 ± 4 years in female and 59 ± 8 years in male (age range, 50 to 72 years). Fig. 1 shows the distribution among age groups in all patients studied. The distribution of extrarenal manifestations of SLE in each patient at presentation is presented in Table 1. Autoimmune hemolytic anemia (AIHA) and musculoskeletal were the two most common systems

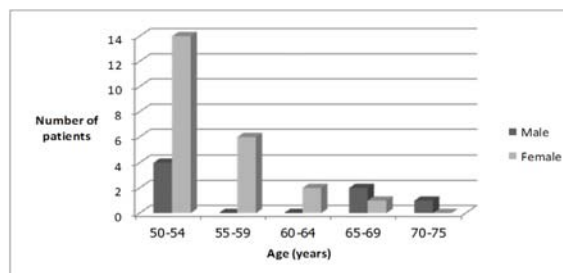


Fig. 1 Age and sex distribution of lupus nephritis patients in Thailand

Table 1. Extrarenal manifestations of all patients at presentation compared with the patients with early onset LN from previous study⁽¹⁰⁾

| | Late onset LN (%) | Early onset LN (%) |
|-------------------------------|-------------------|--------------------|
| Cutaneous system | 3 (10.0) | (66.0) |
| Musculoskeletal system | 10 (33.3) | (62.9) |
| Nervous system | 5 (16.7) | (12.3) |
| Cardiovascular system | 2 (6.7) | (9.0) |
| Respiratory system | 2 (6.7) | (3.7) |
| Anemia | | |
| Coombs' test positive | 12 (40) | (42.2) |
| Coombs' test negative | 18 (60) | (37.9) |
| Antinuclear antibody positive | 28 (93.3) | (90.0) |
| Anti-DNA positive | 15 (50.0) | (67.2) |

involved in the patients studied (40% and 33.3%), respectively. Moreover, 11 cases (36.7%) were diagnosed as lupus nephritis from renal histological study without other extrarenal signs and symptoms.

Table 2 shows the renal manifestations of the studied patients. Overall, edema was the most frequent finding, observed in 96.6% of the patients. Hypertension (defined as blood pressure $> 140/90$ mmHg in repeated measurements) was reported in 66.7% of all patients. Moreover, 96.6% had proteinuria greater than 0.5 g/day and 63.3% had nephrotic-range proteinuria (> 3.5 g/day). A large proportion of patients had renal insufficiency at presentation as defined by either serum creatinine greater than 1.5 mg/dL (41.3%) or creatinine clearance less than 50 ml/min (70%). All thirty patients underwent renal biopsy for the histopathologic examination.

Table 3 shows the renal histopathologic data according to the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS). Diffuse proliferative glomerulonephritis (class IV) was found in the majority of patients (63.3%), while class V

Table 2. Clinical and biochemical data of renal manifestations of the patients

| | Late onset LN (%) | Early onset LN (%) |
|----------------------------------|-------------------|--------------------|
| Edema | 29 (96.6) | (72.8) |
| Hypertension | 20 (66.7) | (32.4) |
| Urinalysis | | |
| Nephrotic | 6 (20.0) | (27.5) |
| Nephritic | 0 | (34.8) |
| Nephrotic/nephritic | 24 (80.0) | (28.6) |
| 24-hr urinary protein excretion | | |
| < 0.5 g/day | 1 (3.3) | (9.0) |
| 0.5-3.5 g/day | 10 (33.3) | (47.4) |
| > 3.5 g/day | 19 (63.3) | (43.6) |
| Serum creatinine > 1.5 mg/dL | 12 (41.3) | (41.3) |
| Creatinine clearance > 50 ml/min | 9 (30) | (42.0) |
| 25-50 ml/min | 13 (43.3) | (33.0) |
| < 25 ml/min | 8 (26.7) | (25.0) |

Table 3. Histopathologic findings in 30 patients compared with the patients with early onset LN from previous study⁽¹⁰⁾

| ISN/RPS 2003 classification | Late onset LN (%) | Early onset LN (%) |
|-----------------------------|-------------------|--------------------|
| Class I LN | 0 | (1.0) |
| Class II LN | 0 | (15.9) |
| Class III LN | 2 (6.7) | (3.5) |
| Class IV LN | 19 (63.3) | (61.5) |
| Class V LN | 6 (20.0) | (15.6) |
| Class III + V LN | 1 (3.3) | 0 |

was found in 20%.

During the follow-up period 25.8 months (range, 6 to 96 months), 4 patients died. Infection was the leading cause of death (75%) [2 patients died from pneumonia with adult respiratory distress syndrome, 1 patient died from cryptococcal meningitis with candidemia, the last one died from multiple cerebral infarction from vasculitis].

By life-table analysis, the probability of patient survival was 94.1% at 12 months, 68.6% at 36 months and 34.3% at 60 months. Fig. 2 shows the probability of survival for the entire patient cohort.

Discussion

Lupus nephritis is a relatively common renal disease and is prevalent in Thailand. Affected

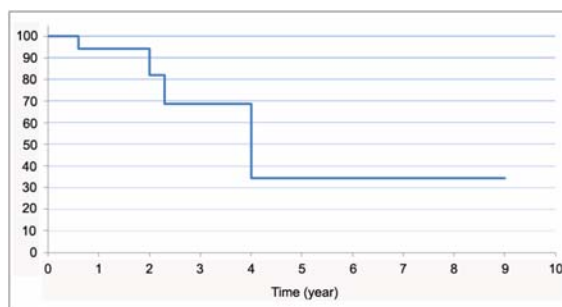


Fig. 2 Probability of survival in lupus nephritis patients and number of patients followed during each time period

individuals are mostly female teenagers or adolescents. Shayakul et al⁽¹⁰⁾ reported the clinicopathological findings and outcome in 569 patients with lupus nephritis in Thailand. The female to male ratio was 10:1 (female 515 and male 54) and the mean age was 28 ± 10 years. In the present series, female patients represented 76.6% of cases in the late-onset lupus nephritis group. The female to male ratio of 3.3 was significantly lower than the ratio of 10 that observed in the early-onset group from previous study⁽¹⁰⁾. Most of the literature data indicated that the sex ratio declines with age in SLE⁽³⁾. This probably reflects the relationship between SLE and estrogen status⁽³⁾. It has been reported that patients with late onset lupus may constitute a specific SLE subgroup^(2,12). These patients seem to have a more insidious onset, be less likely to have major organ involvement and have less degree of disease activity^(3,4). It was found in this retrospective study⁽⁴⁾ that patients with late onset lupus nephritis constitute a small group of lupus nephritis (1.96%) and these patients did not exhibit a great difference in clinical or pathological features compared with early onset lupus nephritis^(2,4). The clinical presentation in patients with late onset SLE varied in different reports. Mak A et al⁽¹²⁾ observed that the serositis was more frequent, while malar rash, photosensitivity and alopecia were less frequent in older SLE patients. According to several authors, skin manifestations, photosensitivity, arthritis and nephritis, occur rarely in the elderly patients with late SLE onset; prevalence of serositis, lung involvement and Sjogren's syndrome were observed more often^(3,4,7). Late onset SLE patients manifested higher rate of positive findings of rheumatoid factors, as well as of anti-Ro and anti-La antibodies; and the lower occurrence of anti-RNP antibodies and hypocomplementaemia. A slow onset of the disorder, non-specific manifestations at the beginning of the

illness and less frequent prevalence of SLE in the elderly often result in late diagnosis. Our patients with late onset LN showed a tendency toward greater prevalence of autoimmune hemolytic anemia (AIHA) and musculoskeletal symptoms, while the cutaneous and cardiovascular symptoms were less common than that in the early-onset LN patients⁽¹⁰⁾. In present study, there was a higher occurrence of edema, hypertension, nephrotic range proteinuria and renal dysfunction in patients with late onset LN than in those with early onset LN⁽¹⁰⁾. One-fourth of the patients the authors studied had initial creatinine clearance less than 25 ml/min. Mak A et al reported that the late onset SLE patients had significantly lower creatinine clearance and were more likely to be hypertensive⁽¹²⁾. The histological findings were rarely mentioned in literature. A few detailed data demonstrated the rarity of severe proliferative nephritis in patients with late onset SLE⁽³⁾. The authors found that type IV LN was the most frequent finding, the same as in those with early onset LN. These data suggested that the patients with late onset lupus nephritis share similar histological lesions as the early onset lupus nephritis patients. In the late onset LN group, the authors observed a survival probability of 94.1% at 12 months, 68.6% at 36 months, and 34.4% at 60 months, versus 84% at 12 months, 80.1% at 36 months and 76.5%, respectively, in the early onset group⁽¹⁰⁾. Infection was the leading cause of death, the same as in those patients with early onset LN.

Conclusion

Lupus nephritis in elderly patients is not uncommon. The late onset LN patients had a higher incidence of hypertension and renal dysfunction. The prompt diagnosis of LN should be made for proper management and excellent outcome.

Potential conflicts of interest

None.

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การศึกษาลักษณะอาการทางคลินิกและผลพยาธิสภาพชิ้นเนื้อไตในผู้ป่วยสูงอายุที่เป็นโรคไตอักเสบชนิด lupus nephritis ในโรงพยาบาลศิริราช

มนตรี กอบกิจเจริญ, ธัญญารัตน์ อธิพรเลิศรัฐ, รัตนา ชวนะสุนทรพจน์, ทวี ชาญชัยรุจิรา, นพรัตน์ เลาวหุตานนท์, ไพศาล ปารีชาติกานนท์, บุญยฤทธิ์ ชื่นสุขน

วัตถุประสงค์: เพื่อศึกษาลักษณะอาการทางคลินิก ผลการตรวจทางห้องปฏิบัติการที่มีความสัมพันธ์กับโรค และผลพยาธิสภาพชิ้นเนื้อไตรวมทั้งการพยากรณ์โรคของผู้ป่วย lupus nephritis (LN) ที่มีอายุมากกว่าหรือเท่ากับ 50 ปี

วัสดุและวิธีการ: ได้ทำการรวบรวมบันทึกข้อมูลทางคลินิกของผู้ป่วย LN ในโรงพยาบาลศิริราชระหว่างปี พ.ศ. 2532 ถึง พ.ศ. 2549 จำนวน 30 ราย โดยรวบรวมจากเวชระเบียนผู้ป่วยนอกและใน ผู้ป่วยทุกรายได้รับการตัดชิ้นเนื้อไตโดยผลทางพยาธิวิทยาใช้เกณฑ์ของ International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003

ผลการศึกษา: ได้รวบรวมผู้ป่วย LN จำนวน 30 ราย เป็นหญิง 23 ราย และเป็นชาย 7 ราย ได้รับการติดตามผลการรักษาเฉลี่ย 25.8 เดือน (6 เดือนถึง 96 เดือน) ผู้ป่วยมีอายุเฉลี่ย 56.6 ± 4 ปี ลักษณะอาการทางคลินิกที่พบได้บ่อยได้แก่ ความดันโลหิตสูง 66.7%, ค่าการทำงานของไตผิดปกติ (creatinine มากกว่า 1.5 mg/dL) 41.3%, nephrotic-range proteinuria 63.3%, creatinine clearance น้อยกว่า 50 ml/min เป็นจำนวน 70% ผลพยาธิสภาพชิ้นเนื้อไตส่วนใหญ่พบเป็น lupus nephritis ชนิดที่ 4 โดยพบถึง 63.3% โอกาสที่ผู้ป่วยจะมีชีวิตอยู่รอดอยู่ที่ 94.1% ที่ 12 เดือน, 68.6% ที่ 36 เดือนและ 34.3% ที่ 60 เดือนโดยมีการติดเชื้อเป็นสาเหตุหลักของการเสียชีวิต

สรุป: Lupus nephritis ในผู้ป่วยที่มีอายุมากกว่าหรือเท่ากับ 50 ปีเป็นภาวะที่สามารถพบได้ในเวชปฏิบัติการวินิจฉัยโรคที่ถูกต้องจะนำไปสู่การดูแลที่เหมาะสมและได้ผลที่ดี
