Analysis of Lupus Activity in End-Stage Renal Disease Treated by Hemodialysis
Kazuhiro Okano, Wako Yumura, Kousaku Nitta, Keiko Uchida, Takako Ohnuki, Akira Kawashima and Hiroshi Nihei

Abstract

Objective  The activity of systemic lupus erythematosus (SLE) has been reported to decrease in patients who have developed end-stage renal disease (ESRD). However, extra-renal symptoms attributable to the disease activity are noted, especially during the first year of dialysis. We studied the clinical course and evaluate the disease activity of SLE in patients with ESRD on hemodialysis for more than 6 months.

Subject and Methods  Fourteen patients with SLE who had been initiated on maintenance dialysis at our center between 1982 and 1999 were examined retrospectively. Their clinical details, organ system manifestations, serologic profiles and immunosuppressive treatment regimens were reviewed. Patients with and without postdialysis flares of SLE were compared statistically.

Results  Five patients exhibited 6 SLE flares under treatment with corticosteroids. Two flares occurred within the first year of the initiation of dialysis, and in 1 patient, aggravation of the disease activity was noted 98 months after the initiation of dialysis. Polyarthritis was noted in 5 cases and fever in 4 cases. The serum complement levels decreased in all 6 cases with relapse of SLE activity. Compared with the other 9 patients who did not exhibit SLE relapse, no significant differences were found in 5 patients who did with respect to the demographic and serologic features at the initiation of dialysis.

Conclusion  We conclude that the disease activity does not always burn out in patients of SLE who show progression to ESRD. SLE flares can sometimes occur even after one year of the initiation of dialysis. SLE patients on dialysis should be carefully followed up by clinical and serological monitoring, and treated by appropriate immunosuppressive therapy.

Key words: systemic lupus erythematosus, renal failure, relapse, prognosis

Introduction

Progression of lupus nephritis to end-stage renal disease (ESRD) is a serious complication of systemic lupus erythematosus (SLE). Lupus nephritis occurs in 50% to 80% of SLE patients (1) and has a strong impact on the prognosis; the high morbidity and mortality of patients with SLE are associated with the severity of lupus nephritis (2-4). About 20% of patients progressing to ESRD require maintenance dialysis or renal transplantation within ten years (2, 5). The activity of SLE after the development of ESRD has been reported by several groups (3-9). According to many reports, the activity of SLE after the development of ESRD tends to decline as reflected by the clinical and serological features. Cheigh et al (4) reported that lupus activity was clinically apparent in 55.4% of patients with ESRD during the first year and in 6.5% during the fifth year. It was believed that the disease became inactive within ten years of the development of ESRD. This so-called "burn-out" phenomenon was first described by Fries et al (6). However, SLE flare during dialysis is also not rare. Some investigators reported that several risk factors could predict the persistence of activity of SLE (4, 5, 7). In the present report, we describe the results of a retrospective study performed to evaluate clinically and serologically the activity of SLE in patients with ESRD on maintenance hemodialysis therapy.

Patients and Methods

Between 1982 and 1999, we treated 14 patients with ESRD secondary to lupus nephritis by hemodialysis for more than 6 months at the Kidney center of Tokyo Women's Medical University. Patients who were dialyzed for less than 6 months because of recovery of renal function or patient death were excluded from this study. The records of the 14 patients were retrospectively reviewed for data on the clinical and laboratory markers of disease activity while under hemodialysis for ESRD. Clinical flares were defined as organ symptoms associated with serological changes such as decrease in serum complement level or increase in anti-double stranded DNA (dsDNA). Organ
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Symptoms included rash, discoid lupus, photosensitivity, oral ulcers, polyarthritis, serositis, seizures, and fever not caused by infection. Multiple organ system involvements noted at the same time were counted as a single episode of flare. The serological tests for lupus activity, including antinuclear antibody (ANA), anti-dsDNA, serum total complement (CH50), serum complement 3 (C3) and serum complement 4 (C4), had been studied routinely, or more frequently when clinically indicated. SLE flares were treated mainly by the increase of corticosteroids sometimes with the other immunosuppressants, such as cyclophosphamide or azathioprine.

Patients were divided into two groups according to whether or not they developed a SLE flare. Group 1 consisted of patients exhibiting a flare after the initiation of hemodialysis, and group 2, those who did not develop any flare. The demographic, organ system involvement, serological profiles and immunosuppressive treatment were compared between the two groups. Values are presented as means ± standard deviation. Statistical analysis of dependency was performed by Student's t-test and the chi-square test. Differences were considered significant when the corresponding p values were <0.05.

Results

The demographic data of the study subjects are shown in Table 1. All 14 patients were female; 11 patients had undergone renal biopsy, of which 10 showed diffuse proliferative lupus nephritis (WHO class IV) and 1 showed membranous lupus nephritis (WHO class V) [data not shown]. Five patients (36%) exhibited a SLE flare after the initiation of maintenance dialysis. The mean age at the diagnosis of SLE and at the initiation of dialysis were almost the same between the two groups. The interval between the diagnosis and the initiation of dialysis was 112.2±60.3 months (range 7 to 160) in group 1 and 199.9±101.5 months (range 42 to 368) in group 2. Despite the wide difference of mean values between the two groups, the differences did not reach statistical significance. Two patients had died: one from group 1 died of myocardial infarction and the other from group 2, of cerebral hemorrhage. Kidney transplantation was performed in 1 patient from group 2, who had been maintained by hemodialysis for 12 months. The serological activity at the initiation of dialysis in these subject is shown in Table 1. In group 1, the mean serum complement levels were slightly lower than those in group 2. The serum C3 level at the initiation of dialysis decreased slightly in both groups. In group 1, the serum C3 level continued to be low at one year after the initiation of dialysis. Other serological data showed no significant differences between the two groups. There were 6 flares in 5 patients. The interval between the initiation of dialysis and the diagnosis of SLE flare decreased slightly in both groups. In group 1, the serum C3 level continued to be low at one year after the initiation of dialysis. Other serological data showed no significant differences between the two groups. There were 6 flares in 5 patients. The interval between the initiation of dialysis and the diagnosis of SLE flare varied widely (3 to 98 months). Two of 6 flares were diagnosed in the first year of dialysis. In the present study, there was no tendency for SLE flare to occur during the first year after the initiation of dialysis. Immunosuppressive therapy was administered in all 6 cases when the disease became active. The dose of corticosteroids at the initiation of dialysis was almost the same. Total dose of steroids for one year from the initiation of dialysis also had no wide difference. Cyclophosphamide was administered in 1 patient in group 1. Steroid pulse therapy at the initiation of dialysis was carried out for two patients in group 1 and one patient in group 2. Thus, almost the same

Table 1. Demographic and Immunological Data of SLE patients

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (male: female)</td>
<td>5 (0.5)</td>
<td>9 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis of SLE, yrs, (range)</td>
<td>23.2±6.2 (15–30)</td>
<td>24.3±9.0 (14–41)</td>
<td>NS*</td>
</tr>
<tr>
<td>Age at initiation of dialysis, yrs, (range)</td>
<td>34.0±6.4 (27–42)</td>
<td>38.2±6.8 (29–48)</td>
<td>NS*</td>
</tr>
<tr>
<td>Duration of SLE before dialysis, mo, (range)</td>
<td>112.2±60.3 (7–160)</td>
<td>199.9±101.5 (42–368)</td>
<td>NS*</td>
</tr>
<tr>
<td>CH50 at initiation of dialysis, U/ml</td>
<td>32.28±13.90</td>
<td>34.39±9.53</td>
<td>NS*</td>
</tr>
<tr>
<td>C3 at initiation of dialysis, mg/dl</td>
<td>47.76±23.36</td>
<td>58.24±11.08</td>
<td>NS*</td>
</tr>
<tr>
<td>C4 at initiation of dialysis, mg/dl</td>
<td>30.00±10.49</td>
<td>32.76±16.25</td>
<td>NS*</td>
</tr>
<tr>
<td>dsDNA titer at initiation of dialysis</td>
<td>19.80±17.66</td>
<td>1.05±0.34</td>
<td>NS**</td>
</tr>
<tr>
<td>CH50 at 1 year later from initiation, U/ml</td>
<td>33.8±9.8</td>
<td>37.9±5.1</td>
<td>NS*</td>
</tr>
<tr>
<td>C3 at 1 year later from initiation, mg/dl</td>
<td>46.4±11.0</td>
<td>73.9±15.3</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td>C4 at 1 year later from initiation, mg/dl</td>
<td>30.7±8.7</td>
<td>31.1±12.7</td>
<td>NS*</td>
</tr>
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</table>

There is no significant difference in demographic profile between the two groups. The serum complement 3 level at 1 year after the initiation of dialysis was the only parameter which showed a significant difference. *Student’s t test, **chi-square test.
regimens of immunosuppressive therapy were administered for the two groups. In group 1, the mean dose of corticosteroids administered was 8.75±4.11 mg/day before the diagnosis of SLE flare, and 18.33±9.31 mg/day when the disease became inactive again. Patients with SLE flares were treated by intravenous steroid pulse or augmented oral steroids.

Discussion

Previous reports demonstrated that the activity of SLE decreased after the initiation of chronic dialysis in patients with ESRD despite the reductions in immunosuppressive therapy (6). In 1984, Pahl et al (7) reported that the disease activity of SLE persisted in six of 11 patients after the initiation of dialysis. Several investigators also reported that the disease activity persisted in some SLE patients at least during the first year of dialysis (3, 4, 7, 8). However, many clinicians believe that SLE becomes less active or burns out after the development of ESRD. On the other hand, it is still uncertain whether the “burn-out” phenomenon is dependent on the uremic state or on treatment by dialysis. Moreover, the lupus activity may reflect the natural disease course of SLE, which seems to show a gradual wane (8–11). Investigation of the lupus activity is fraught with difficulties, especially in patients with uremia. It is difficult to determine what should be considered as SLE activity and what is related to renal failure or dialysis. Despite our best effort in clinical judgement, the definition of flare is inevitably arbitrary. There are over 60 systems for defining and evaluating the disease activity of SLE. The British Isles Lupus Assessment Group (BILAG) scale, the University of Toronto SLE Disease Activity Index (SLE-DAI), and Systemic Lupus Activity Measure (SLAM) have been shown to demonstrate the best inter-visit and inter-rater reliability (12). Nevertheless, the scales are not always suitable for retrospective studies. For example, SLAM consists of 24 clinical items and 7 laboratory items and SLE-DAI, 24 clinical items and 7 laboratory items. Because too many parameters were required, we could not apply these scales for the judgement of the disease activity of SLE. Szeto et al (5) thought SLE was active, when the patient complained of one or more clinical symptoms with changes of immunological parameters. In this context, we defined disease activity as being high when the patients complained of symptoms of organ involvement associated with changes in immunological parameters. These data are thought to be objective measures of the disease activity. There are problems that often result in overestimation of the disease activity of SLE, but the extent of misjudgment of the activity can be decreased by the use of immunological data.

In our study, we found that five of 14 patients developed clinical features of active lupus. In 2 patients, the SLE flare occurred in the first year of dialysis, and one patient exhibited SLE flare at 98 months after the initiation of dialysis, although hemodialysis was initiated only 7 months after the diagnosis of SLE. Lupus activity, therefore, can remain persistent even after the patient progresses to ESRD. Younger patients are reported to more frequently have persistent activity of SLE after the initiation of dialysis (5). However, we found no statistically significant relationship between the age at diagnosis of SLE and the persistence of disease activity. The racial and socioeconomic differences were precisely examined in some studies (13–17); in the present study, since we selected only Japanese patients as the subjects of our investigation, we paid little attention to these factors. One patient (case 3 in Table 2) refused to take high dose of oral steroids and we had to therefore taper the drug dose rapidly. Death of patients under dialysis for over 6 months was in most cases caused by infection or cardiovascular disease rather than by active lupus (8, 9). With the improvement in immunosuppressive therapy regimens, death caused by infection has become less frequent. In the present study, it was not necessary to show much concern for infection.

The serological data did not show much correlation with the prognosis of SLE. At the initiation of dialysis, both groups showed a slightly low level of serum C3. It may mean that SLE activity is not always diminished in the patient at the stage of ESRD. One year after the initiation of dialysis, the serum C3 levels were significantly lower in group 1 than in group 2. It is difficult to explain the time-course difference between two groups from viewpoint of epidemiology. In two cases of group 1, the follow-up period after the initiation of dialysis is about 1 year. So we evaluated the serological difference between the two groups at 1 year after the initiation of dialysis. We did not
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Figure 1. Interval between the onset of SLE and the initiation of hemodialysis. Group 1 consists of 5 patients (case 1–case 5) and group 2 of 9 patients (case 6–case 14). Six SLE flares are observed in 5 patients but only 2 flares occurred in the first year of dialysis.

find a significant difference of age at the initiation or the duration of SLE before dialysis and the serological data at the initiation of dialysis. Five of 14 cases experienced the increase of SLE activity, were always accompanied with the decrease of complement levels. We think that the misjudgement of the disease activity happens less frequently with use of immunological data. These findings suggest that the disease activity of SLE does not always diminish after the initiation of dialysis. The serum ANA titers were markedly and persistently elevated in 2 patients. However, we consider that the serum ANA titers show lower specificity for the disease activity than serum complement level, because some patients without SLE flare also had mild but persistent elevation of the serum ANA titer.

Polyarthritis was the most frequent manifestation, but it is in general a typical complaint among patients under maintenance dialysis. In the present study, we took it as a symptom of SLE when it was also associated with a serological abnormality. Fever was also a frequent manifestation observed. It may be dangerous to think that only one clinical symptom such as polyarthritis or fever reflects the disease activity. But the combination of clinical findings and laboratory data can increase the reliability of judgement of the disease activity.

Immunosuppressive therapy was continued in five of the 6 cases in whom SLE became active. In all cases, the dose of corticosteroids was increased when the disease became active. The manifestation of organ system involvement and the serological data improved with therapy.

The majority of studies supported the tendency toward decreased clinical and serological lupus activity following ESRD. The need for immunosuppression or high dose prednisone was decreased in this stage. This phenomenon is called “burn out”. There are some possibilities to explain this phenomenon. These include depressed cellular and humoral immunity in ESRD (6–8), removal of lupus factors by dialysis (7, 9), or a natural outcome in SLE discernable only by prolongation of life past ESRD (4, 7). Recently, there are some reports that SLE activity is
prolonged in ESRD. Nossent et al (1) were the first to call attention to the disease activity of SLE after ESRD. They concluded that the disease activity diminished during dialysis but not abolished. Szeto et al (5) reported that nine out of 18 patients had active lupus in their first year of dialysis, and four of them remained active during the second year. Krane et al (13) showed that SLE did not always burn out in patients who reached ESRD. They also suggested that the difference in relapse had an association with the patient populations. As the treatment for ESRD progressed, the mortality of the patient with both the persisted activity of SLE and ESRD was decreased. It may contribute to the increase of SLE relapse during dialysis.

In conclusion, we found that the disease activity of SLE does not always diminish in patients who show progression to ESRD. Postdialysis flare of SLE can occur even after one year of the initiation of dialysis. Polyarthritis was the most frequent organ system manifestation. There was no good indicator predictive of SLE flare among the demographic and serological features. With improvement in SLE therapy, death caused by postdialysis flare or by immunosuppression, has become rare. On the other hand, the number of deaths related to long-term dialysis has increased in lupus patients. It is recommended that SLE patients on dialysis are followed up carefully by clinical and serological monitoring.

References