Patterns of Systemic Lupus Erythematosus in the Intensive Care Unit and Causes of Mortality

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Abstract. The aim of this study was to investigate the causes, clinical course and the outcomes of critically ill lupus patients requiring emergency admission to the intensive care unit in patients with Systemic Lupus Erythematosus. A retrospective study was conducted at King Abdullah University Hospital, Jeddah, in the western region of Saudi Arabia, which included all critically ill patients with Systemic Lupus Erythematosus who were admitted to the intensive care unit over a seven-year period. The demographic features, causes of intensive care unit admission, duration of intensive care unit hospitalization and outcome were recorded and compared statistically. A total of 30 patients were included in this study. The most common causes of admission were abnormal complete blood count (65%), fever (65%, renal involvement (65%), hypertension (60%), infection (50%), lung (50%), mucocutaneous (40%), musculoskeletal (30%), neurophysiologic (20%), and cardiovascular (20%) involvement. Mortality rate was 48% and was significantly associated with septic shock (P=0.001), lung hemorrhage (P=0.001) and thrombocytopenia (P=0.001). The mortality rate in critically ill Systemic Lupus Erythematosus patients was high. Patients who had septic shock, lung hemorrhage and thrombocytopenia significantly increased the likelihood of dying.

Keywords: Systemic lupus erythematosus, Intensive care unit, Causes of mortality.

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Introduction

Systemic Lupus Erythematosus (SLE) is a chronic, multisystem autoimmune disorder that provokes inflammation in various organs of the body. The inflammation is due to the production of antibodies that attack cells of host organs, including the skin, muscles, joints, blood, kidneys, and the brain. The disease persists for life and is characterized by sudden flare-ups, repeated life-threatening infections, mild-to-severe kidney impairments, repeated miscarriages, strokes, and, sometimes, permanent disability and death. Although the specific cause of SLE is unknown, multiple factors are associated with the development of the disease. These include genetic, racial, hormonal, and environmental factors. The incidence of SLE also varies according to age, sex, and race. Globally, SLE primarily affects younger women; 9 of 10 patients with SLE are females between the ages of 15 and 45 years[1,2].

The disease often begins at menarche and many women with SLE experience sudden flare-ups during specific phases of the menstrual cycle or shortly after delivering a baby[3-5]. Although SLE is not prevalent in men, among patients who have the disease, renal, neurological, hematological and vascular outcomes are more severe in men than in women[6]. The pathogenesis of SLE is insidious and a definitive diagnosis may take up to 10 years, so organ damage is often severe by the time the diagnosis is confirmed.

Estimations of the exact incidence of SLE are variable. Some reports indicate that because of improved diagnostic measures, the incidence of SLE is increasing. For example, in a study covering a span greater than 40 years, Uramoto et al.[6] found that the pooled incidence of SLE had more than tripled from 1.51 per 100,000 during 1950 to 1979 to 5.56 per 100,000 during 1980 to 1992. In a recent review of 19 studies published from 1995 to 2000, Ruiz-Irastorza et al.[6] reported an even higher incidence rate: 7.3 per 100,000. The frequency of SLE is much higher among first-degree relatives of patients who have either SLE or other autoimmune disorders than among the general population. Many immune disturbances occur in SLE. Antinuclear antibodies (ANAs) are present in the serum in virtually all patients with active SLE, and antibodies to native Double Strand Deoxyribonucleic Acid (dsDNA) are relatively specific for the diagnosis of SLE. SLE is also classified as a Type III hypersensitivity reaction[9].
The major pathophysiological phenomenon in this type of hypersensitivity reaction is the formation of antigen-antibody complexes, called immune complexes. Immune complexes in SLE contain IgM, IgG, and IgA. Deposition of immune complexes is accompanied by the activation of the complement system, the very potent nonspecific defense mechanism involved in inflammation and infection. Complement proteins have a chemotactic affect on neutrophils, drawing these cells to the site of inflammation. In an attempt to eliminate the immune complexes, neutrophils release lysosomal enzymes, which damage local tissues. In SLE, the deposition of the immune complexes and subsequent complement activity initiate pathological changes. Immune complexes have a high affinity for vessel walls and the glomerular basement membrane of the kidneys. The changes caused by their deposition in these areas can progress and cause organ damage in such vital organs as the kidneys, lungs, and heart. Exacerbations in SLE requiring ICU admission may result from acute or persistent disease activity, the side effects of treatment, or both. The disease activity is directly associated with specific organ damage such as cardiovascular and cerebrovascular diseases, pulmonary hypertension, renal failure, and skin lesions.

**Method**

**Study Design, Population and Setting**

This was a retrospective study of the intensive care unit (ICU) at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia. The study included all patients with a diagnosis of SLE admitted to the ICU from September 1999 to August 2006. A total of 30 SLE patients out of 4,694 patients were admitted during that period (0.6%).

**Data Collection and Statistical Analysis**

Diagnosis of SLE was confirmed if the patient fulfilled at least four of the 1982 American Rheumatism Association revised classification criteria. The following clinical and laboratory parameters were registered: demographic features, underlying diseases and associated manifestations of SLE, causes of admission, complete blood count, renal function tests, coagulation and autoimmune profiles, characteristics of lesions on chest radiographs, sites of infection and organisms cultured.
treatments administered during the patient's ICU stay, occurrence of complications, duration of ICU stay and outcome. The cause of ICU admission was defined as the major problem necessitating admission to the ICU. This was determined on the basis of clinical data. Cardiogenic pulmonary oedema is due to poor cardiac performance. Noncardiogenic pulmonary oedema is due to fluid overloading of a noncardiogenic cause. Renal involvement was defined, as urinary excretion of more than 500 mg protein/24 hours, cellular casts not attributable to infection, or abnormal histology on renal biopsy. Abnormal complete blood count was defined as hemolytic anemia or leukopenia (<4 $\times$ 10^9/l) or thrombocytopenia (<100 $\times$ 10^9/l) in the absence of offending drugs. Pneumonia was defined as new and persistent radiographic opacity, positive sputum culture and any three of the following body temperature above 38$^{\circ}$C, white blood cell count above 15 $\times$ 10^9/l, increased airway secretions, or worsening gas exchange[2]. Acute respiratory distress syndrome (ARDS) was defined in accordance with the American-European Consensus Conference on ARDS[3].

Sepsis and septic shock were defined in accordance with the criteria of Bone and coworkers[4]. Hypertension (patient is known hypertensive or receiving antihypertensive agents or BP > 140/90 mmHg on more than one occasion), neuropsychiatric involvement was defined according to the American College of Rheumatology (ACR) revised criteria[5,6], neurological involvement (headache, seizures, focal signs, strokes, chorea, aseptic meningitis, parkinsonism, peripheral neuropathy) and psychiatric involvement (depression, mania, delirium, dementia, cognitive difficulties)[5,6].

Finally, patient outcome was clussed as death while the patient was in the ICU or survival to discharge from the ICU.

Data analysis was done using statistical package for Social Sciences Software (SPSS)[7]. Mean ± SD was calculated for quantitative data and proportions for categorical variables. One-way analysis of variance (ANOVA) and 'Student's' t-test were used for comparing means of continuous variables. Proportions were compared by Chi-square test and Mantel-Haenszel test, if needed. Multiple logistic regression analysis was performed to test for the independent effect of different variables. Significance level was set at <0.05 throughout the analysis.
Results

From September 1999 to August 2006, a total of 4,694 patients were admitted to the ICU. Of these, thirty SLE patients were included in the present study. They required 43 ICU admissions. There were 9 patients with more than one admission to the ICU including 5 patients with 2 admissions and 4 patients with 3 admissions. Age range was 9-46 years (24.4 ± 10.3) with a female predominance of 14:1. Their ICU duration was 2-55 days (15.5 ± 11.5). Table 1 shows the major causes of ICU admissions. The most common presentation during their ICU admission was abnormal complete blood count (26 [87%]); anemia was found in 12 patients, thrombocytopenia affected another 12 patients and another 2 patients had leukocytosis. 25 (83%) of the patients were febrile. Renal system involvement was seen in 24 (80%), and hypertension was present among 18 (60%). Infections were the cause of admission in 16 (53%). Respiratory system involvement was 15 (50%), mucocutaneous manifestation was found in 13 (43%), joints involvement in 9 (30%), and neuropsychiatry involvement in 8 (27%). Patients in the cardiogenic category were 7 (23%) and 5 (17%) with coagulopathy in the form of bleeding while 4 (13%) developed recurrent thrombotic episodes. 11 (69%) of infectious causes was pulmonary in origin and 9 (31%) were extra pulmonary (disseminated tuberculosis and septicemia). Respiratory system involvement was in the form of pneumonia with ARDS in 8 patients, lung hemorrhage in 3 patients, confirmed positive pleural effusion culture in 3 patients, and one patient with negative pleural effusion culture. For patients in the neurological category, repeated seizures were the most common cause of admission. Acute stroke (2 infarction and 2 intracranial bleeding) was the underlying diagnosis in 4 patients. Patients with cardiovascular involvement included 5 with pulmonary oedema (2 cardiogenic, 3 noncardiogenic), 1 with pericardial effusion and one with cardiac tamponade. Of those with bleeding diathesis, 3 had lung hemorrhage and 2 had intracranial bleeding (only 1 patient was on anticoagulant). Antinuclear antibodies (ANA) and anti-dsDNA were positive in 97%, and 60%, respectively. The anti-phospholipid antibodies were detected among five patients (17%).
Table 1. Reasons for admission of patients with systemic lupus erythematosus (SLE) to intensive care unit.

<table>
<thead>
<tr>
<th>System involvement</th>
<th>Total number of patients N (100%)</th>
</tr>
</thead>
</table>
| Hematological system involvement | Yes 26 (83%)  
No 4 (13%)                     |
| Fever                         | Yes 25 (83%)  
No 5 (17%)                      |
| Renal system involvement      | Yes 24 (80%)  
No 6 (20%)                       |
| Hypertension                  | Yes 18 (60%)  
No 12 (40%)                      |
| Infectious causes             | Yes 16 (52%)  
No 14 (48%)                      |
| Respiratory system involvement| Yes 15 (50%)  
No 15 (50%)                      |
| Skin involvement              | Yes 13 (43%)  
No 17 (57%)                      |
| Musculoskeletal system involvement | Yes 9 (30%)  
No 21 (70%)                     |
| Neuropsychiatric involvement  | Yes 8 (27%)   
No 22 (73%)                      |
| Cardiovascular system involvement | Yes 7 (23%)  
No 23 (77%)                     |
| Bleeding diathesis            | Yes 5 (17%)   
No 25 (83%)                      |
| Thrombosis                    | Yes 4 (13%)   
No 26 (87%)                      |

As in Table 2, which represents the most common causes of mortality, the mortality rate was high (12 [40%]). Multivariate logistic regression analysis showed that the presence of septic shock, hemorhagic lung, and thrombocytopenia increased the likelihood of dying and it was statistically significant (P-value 0.00, 0.02, 0.05), whereas other causes of ICU admissions had no influence.
Table 2. Causes of death for patients with systemic lupus erythematosus (SLE) in the intensive care unit and their significance to mortality rate.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Total number of patients N (100%)</th>
<th>Mortality</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (%)</td>
<td>No (%)</td>
<td></td>
</tr>
<tr>
<td>Total mortality</td>
<td>12 (40%)</td>
<td>12</td>
<td>18</td>
</tr>
<tr>
<td>Septic shock</td>
<td>12 (40%)</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Long hemorrhage</td>
<td>3 (10%)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12 (40%)</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Neuropsychiatry</td>
<td>8 (27%)</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>15 (50%)</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (60%)</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>4 (13%)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>7 (23%)</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Brain hemorrhage</td>
<td>2 (7%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Renal failure</td>
<td>24 (80%)</td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>

Discussion

The number of SLE patients who required ICU admission was high (6/1000) compared to that in other studies[1,4,12]. This could be explained firstly by the fact that aggressive SLE is more common in women of reproductive age[14], and 93% of our patients were females with an age range of (24 ± 10). Secondly, the majority were non-white patients[13], there were different races in our hospital and most of them were non-Caucasians (Asian and African in origin).

Factors that bring patients with SLE to the ICU; however, differs from those that contribute to mortality. In this study, cytopenia was the highest cause of ICU admissions (87%) of patients whether associated with fever (83%) or not, while some studies support this present study's findings that cytopenia is a leading cause of morbidity[15], other studies did not. Ansell et al[14] found that infection followed by acute renal failure were the most common reasons of ICU admissions, while Thong et al[10] found infection, hypotension due to sepsis and acute respiratory failure were the most common reasons for ICU admission. Fever can be a
sign of disease activity (47%) or as part of an infectious process (53%). Renal involvement (80%) was common among this present study’s patients; kidney biopsy was done for half of them (Stages 3 and 4). Renal biopsy confirmed the presence of lupus nephritis, aids classification of SLE nephritis, and guides therapeutic decisions. Table 3 shows The World Health Organization (WHO) classification for lupus nephritis based on light microscopy, electron microscopy, and immunofluorescence findings. Respiratory system infections affected 69% and this finding corroborates the earlier findings of previous studies.

Table 3. International Society of Nephrology 2003 revised classification of SLE nephritis.

<table>
<thead>
<tr>
<th>Class</th>
<th>Minimal mesangial</th>
<th>Mesangial proliferative</th>
<th>Focal proliferative</th>
<th>Diffuse proliferative</th>
<th>Membranous</th>
<th>Advanced sclerosing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal light microscopy findings</td>
<td>Abnormal electron microscopy findings</td>
<td>&lt;50% of glomeruli involved</td>
<td>&gt;50% of glomeruli involved; classified segmental or global; aggressively treated</td>
<td>Predominantly nephritic disease</td>
<td>Chronic lesions and sclerosis</td>
</tr>
</tbody>
</table>

ANA and anti-dsDNA titers were within expected percentages.

Although survival rates improved markedly during the past 5 decades, patients with SLE still die at a rate 3 to 5 times that of the general population. A series of studies of patients with SLE in general indicated distinct mortality patterns in SLE. Deaths that occurred within 5 years of diagnosis were due to active SLE and infection, whereas, those that occurred more than 5 years after onset were due to atherosclerotic complications, end-organ damage (renal, pulmonary) and treatment side effects. Mortality rate in this study was relatively high (40%) but it was less when compared with other studies (47%). The most important factors that influenced the occurrence of death were septic shock, lung hemorrhage and thrombocytopenia. These were documented by statistical calculations which illustrated significant P-values with the above three factors.

There are some limitations to the present study because of the relatively small number of patients included. Also, the retrospective
design and the study lacks some clinical and laboratory information. Further and larger prospective multicenter trial across the Kingdom of Saudi Arabia is recommended to evaluate the mortality rate and to focus on the role of teamwork (internist, rheumatologist, psychiatrist and specific ICU nursing care) in critically ill SLE patients and their effects in improving the outcome and the quality of patient’s life from this serious illness.

Conclusion

The mortality rate in critically ill patients with SLE is high. There were significant causes of mortality in SLE patients admitted to ICU, which were not the most common causes for their ICU admissions.

Acknowledgments

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References


ملخص لدراسة وصفية لمرضى الذنبة الحمراء
في العناية المركزية

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المستكشف، دراسة الحالات الحمرجة يمرضى الذنبة الحمراء، الذين تم علاجهم بالعناية المركزية، وكيفية التأثير على عدد أسباب الدخول للعناية المركزية، وما إذا كانت هذه الأسباب لها علاقة بزيادة نسبة الوفيات لديهم، أو أن هناك عوامل أخرى أدت إلى ذلك. تم دراسة الحالات الحمرجة يمرضى الذنبة الحمراء، الذين تم علاجهم بالعناية المركزية في مستشفى جامعة الملك سعود، في مدى سبع سنوات، وتتم إحصاء أسباب حالات المرس ضد دخولهم للعناية المركزية. وتتم تحديد الأسباب، وتتبع الأسباب التي أجريت لهم، ونسبة الوفيات لديهم، وباستخدام النموذج المتبقي، تم التحقق من أسباب دخولهم للعناية المركزية، وقد أظهرت النتائج، أن هناك العديد من الأسباب المحتملة للوفيات، بما في ذلك الأسباب التحولية (0.0001)، ولن تكن هذه الأسباب من أسباب دخولهم للعناية المركزية، بل الأسباب التي أدت إلى وفياتهم للعناية المركزية. ونسبة الوفيات كانت مرتفعة (0.0403)، وتم التحقق من الأسباب المحتملة للوفيات، التي تختلف عن أسبابهم التي دخلوا بها للعناية المركزية.