
Mortality Study in Puerto Ricans with Systemic Lupus Erythematosus

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Objective. To determine the most common causes of death among Puerto Ricans with systemic lupus erythematosus.

Methods. Chart and record review of all deaths related to SLE complications from 1960 to 1994 at the University of Puerto Rico Hospital.

Results. Out of 662 patients diagnosed with SLE 161 (24%) died. There were 151 (94%) females and 10 (6%) males. Mean duration of disease was 11.5 years. Mean age at death was 37 years. The primary causes

of death were infection in 44 (27%), uremia in 42 (26%), cardiovascular complications in 33 (20%), central nervous system complications in 18 (11%), and pulmonary complications (other than infectious pneumonia) in 12 (7%).

Conclusions. The most common causes of death in SLE were infections and renal disease.

Key words: *Systemic lupus erythematosus, Mortality, Puerto Ricans*

Systemic lupus erythematosus (SLE) is not an infrequent disease in the patient population of the Puerto Rico University Hospital. A recent review of the Rheumatology section consultations and outpatient records revealed that every year about 30 new patients are diagnosed with SLE. It is a multisystemic disease affecting females more frequently than males; the proportion varying with the age the diagnosis is made. In a review of seven series of adult onset SLE totaling 1177 cases, Masi and Kaslow (1) showed a female to male ratio of 8:1. In our setting, the female to male ratio in the third decade of life is 20:1.

Although most patients with SLE die of unrelated conditions, lupus-related mortality is still high. In the 1960's Siegel et al. (2) compared the 5-year survival of blacks, Puerto Ricans, and whites; he found that survival rates were similar among the three groups, ranging between 62.7% and 65.1%. Urman and Rothfield (3) compared the 5-year survival rate during two study periods: 1957-1968 and 1968-1976. Marked improvement in the survival rate was evident throughout the 1970's, they found an increase in survival from 70%

to 93%. This improvement was attributed to better disease understanding, newer antibiotics, the use of C3 and antiDSDNA, monitoring activity and judicious adjustment of steroid doses. Danish studies between 1965 and 1983 reported an 80%, 10-year survival (4). In the period 1975-1984, Reveille et al. (5) at the University of Alabama showed a 5-year survival of 89% and a 10-year survival of 84%. Published studies from the United States demonstrate a higher mortality rate among African Americans and Puerto Ricans than among Caucasians (6). In Puerto Rico, a study of survival rates and causes of death among SLE patients at the University Hospital has not been previously reported. The University Hospital is the center of referral and the only supra-tertiary medical facility of the island. The purpose of this study is to report the causes of death and review the autopsy findings of SLE patients diagnosed at the University Hospital from 1960 to 1994.

Patients and Methods

The study consisted of a retrospective analysis of all medical records at the University Hospital with a primary diagnosis of SLE from 1960 to 1994. In that period, 662 patients were diagnosed with SLE and all of them fulfilled the American College of Rheumatology criteria for the diagnosis of SLE (7). There were 620 females and 42 males, all of them at least 18 years of age at the time of diagnosis. The causes of death were determined by the

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review of autopsy reports, hospital files, clinic protocols, death certificates, and only rarely by correspondence with a primary physician or family member. Causes of death were classified as those by the disease itself or disease-related morbidity. The duration of the disease or survival time was defined as the interval from the time of diagnosis until death. Cumulative survival rates were calculated for all patients, for patients with renal disease, and for patients without renal disease. The autopsies of 57 patients were also reviewed and the results compared to those in the clinical records. Causes of death were ascertained from autopsy reports in 57 (35%) patients. Death certificates, hospital records, and interviews with primary physicians of patients provided the causes of death of the remaining 104 patients.

Results

Of the 662 patients diagnosed with SLE, 161 (24%) died. Of those, 151 were female and 10 were male. The duration of the disease from diagnosis until death ranged from 1 month to 28 years, with a mean of 11.5 years. The mean age at death was 35 years for both females and males. The main causes of death in this group of patients were infections (27%), renal disease (26%), cardiac disease (20%), central nervous system involvement (11%), pulmonary disease (7%), and gastrointestinal disease (3%) (Figure 1). Infections caused 44 deaths: 19

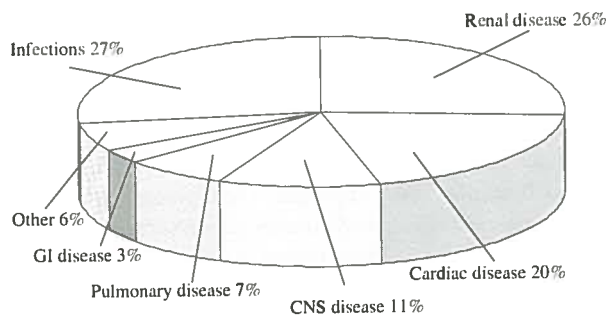


Figure 1. Main causes of death, mortality by organ system complications and infections in patients with SLE.

died of septic shock, 19 died of pneumonia (two by *Pneumocystis carinii*, 1 by *Cryptococcus neoformans*, 1 by *Aspergillus fumigatus*, 1 by cytomegalovirus, 1 by *Nocardia* species), two died of pulmonary tuberculosis, and 2 with bacterial meningitis (Figure 2). Renal involvement was evident in 124 patients, although in not all of them renal disease was the immediate cause of death. Forty-two died of uremia, 29 died of infections, 28 died of cardiac disease, 7 died of pulmonary complications,

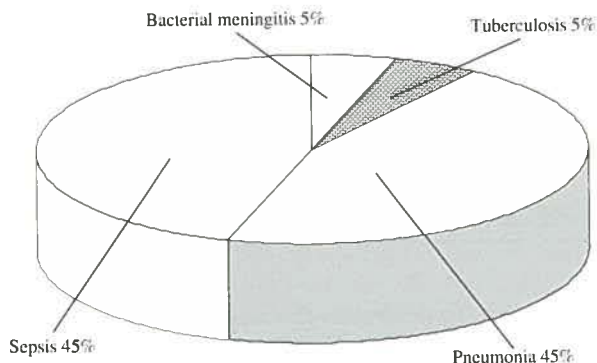


Figure 2. Infections. Deaths related to infectious processes in patients with SLE. Sepsis refers to the presence of a positive bacterial blood culture without an identified focus.

12 died of central nervous system involvement, 4 died of gastrointestinal complications, one died from a diabetic coma and another one died from a severe hemorrhage after a renal biopsy. Seventeen were in end-stage renal disease at the time of death; all of the 10 deceased males had lupus nephritis. The cumulative survival rate of the patients with lupus who had renal disease was 84.7% at 1 year, 71.8% at 5 years and 64% at 15 years and beyond (Figure 3). In contrast, the 5-year and 15-year survival

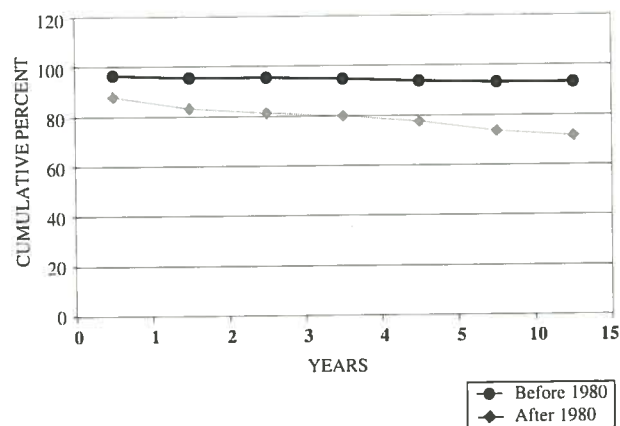


Figure 3. Cumulative survival rate of patients diagnosed before and after 1980. Kaplan-Meier survival curves in measured in years after diagnosis. Survival curve of patients with a diagnosis of SLE prior to 1980 compared to the survival curve of patients diagnosed after 1980.

rate for patients without renal involvement was 94.7% and 94%, respectively. The overall 15-year cumulative survival rate for the group was 76.6%. The patients who died of uremia were classified according to the decade of death. From 1960 to 1970, there were 10 deaths; from 1971 to 1980, there were 22 deaths; from 1981 to 1990, there were 9 deaths; and from 1991 to 1994, there was 1 death (Figure 4).

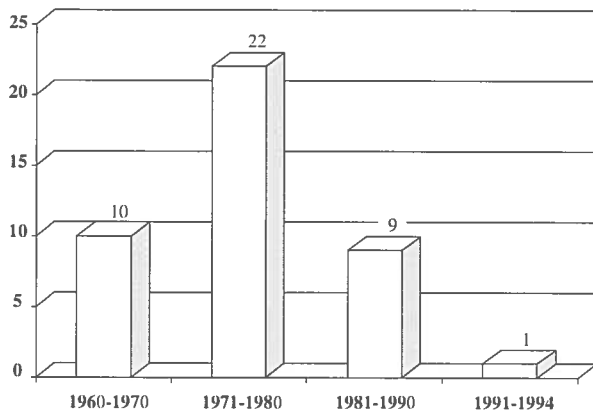


Figure 4. Death from renal failure. Mortality as a direct consequence of the metabolic disturbances caused by renal failure measured in number of patients grouped by the decade in which such death occurred.

There were 33 deaths due to cardiovascular complications: myocarditis in 15 (45%) patients, followed by congestive heart failure in 6 (18%), arrhythmias in 5 (15%), myocardial infarction in 4 (12%), and cardiac tamponade in 3 (9%) (Figure 5). There were 18 deaths

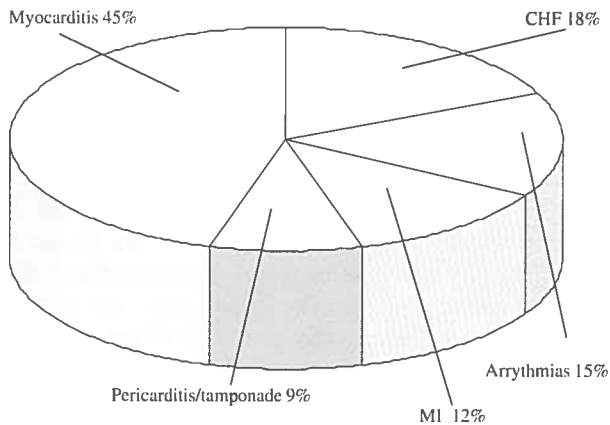


Figure 5. Cardiovascular disease. Mortality as a result of complications of the cardiovascular system. A total of 33 deaths were reported (20 % of all deaths). CHF - congestive heart failure, MI - myocardial infarction.

due to central nervous system complications: 12 (67%) patients had acute cerebritis and 6 (33%) patients had an intracranial hemorrhage (Figure 6). There were 12 deaths due to pulmonary complications: 6 (50%) patients died of pulmonary hemorrhage, 3 (25%) died of by pulmonary embolisms, 2 (17%) died of miliary tuberculosis, and one (8%) from pulmonary tuberculosis (Figure 7). There were

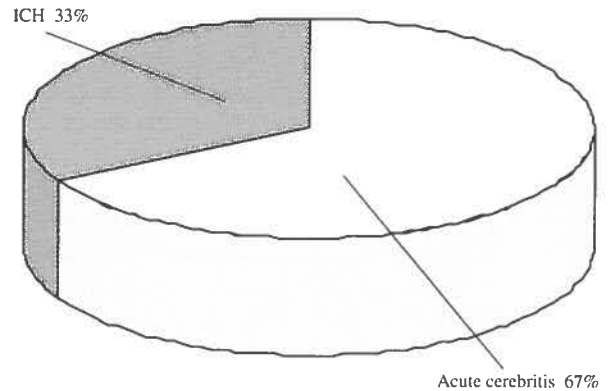


Figure 6. CNS disease. Mortality as a result of complications of the central nervous system. Acute cerebritis is manifested clinically by uncontrolled seizures without a space occupying lesion by imaging or autopsy. A total of 18 deaths were reported (11% of all deaths). ICH - intracranial hemorrhage.

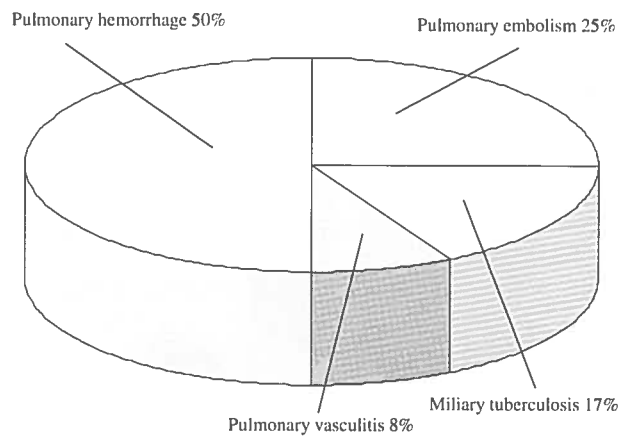


Figure 7. Pulmonary disease. Mortality as a result of pulmonary complications. A total of 12 deaths were reported (7% of all deaths)

5 deaths due to gastrointestinal complications: massive gastrointestinal bleeding in 2 (40%) patients, pancreatitis in 1 (20%) patient, hepatic coma in 1 (20%) patient, and gastric cancer in 1 (20%) patient (Figure 8). One patient died of adrenal hemorrhage and another died from massive bleeding after a renal biopsy.

Of the 161 deaths, 57 autopsies were performed, for a 35% autopsy rate. The findings in these autopsies were: renal pathology in 35 (61%), cardiac pathology in 37 (65%), pulmonary pathology in 39 (68%), central nervous system pathology in 9 (15%) and gastrointestinal disease in 6 (10%) (Figure 9).

Of the 35 autopsies with renal pathology, 29 showed diffuse proliferative glomerulonephritis, the most ominous

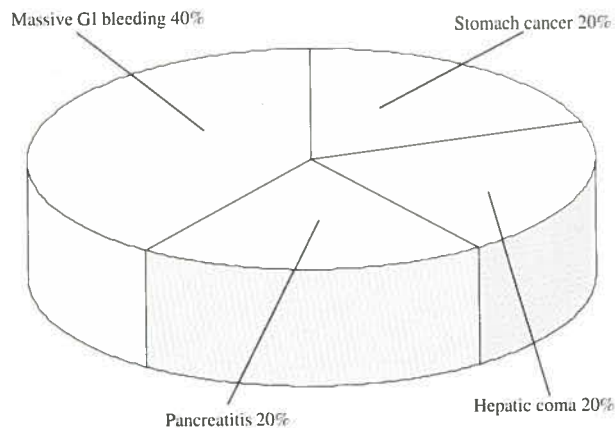


Figure 8. Gastrointestinal/Hepatic disease. Mortality in SLE as a result of complications of the gastrointestinal system. Massive gastrointestinal bleeding was secondary to peptic ulcer disease in the two cases reported. A total of 5 deaths were reported (3% of all deaths).

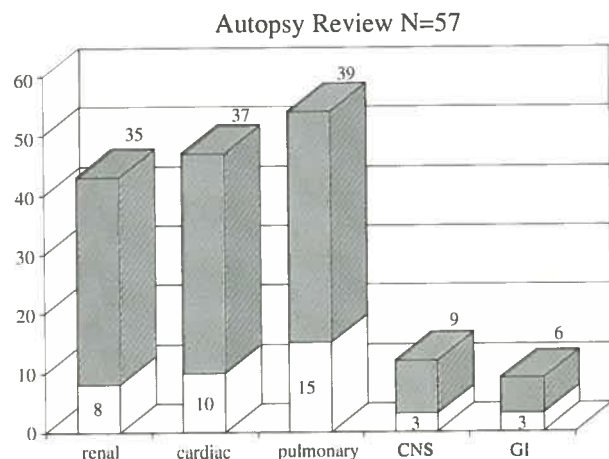


Figure 9. Autopsy review. Number of autopsies demonstrating pathology in the given organ system on the x-axis. The white portion of each vertical bar depicts the number of cases where the organ system complication was the direct cause of death. Each vertical bar demonstrates the total number of autopsies with the presence of pathology in the specified organ .

of all renal manifestations in SLE. However, only 8 of these patients died from uremia. The other patients with diffuse proliferative glomerulonephritis died from sepsis, pneumonia, pulmonary hemorrhage, heart failure, myocardial infarction, arrhythmia, acute cerebritis, meningitis, gastrointestinal bleeding, hepatic coma and massive bleeding after a renal biopsy.

Involvement of the pericardium was observed in 9 autopsies, in 4 patients this was the direct cause of death. Myocarditis was seen in 4 autopsies, in all of them it was

the direct cause of death. Other autopsy findings were: myopericarditis (4 cases) cardiac tamponade due to pericardial effusion (3 cases), cardiomegaly (18 cases), Libman-Sacks endocarditis (9 cases), old myocardial infarction (6 cases) and arteriosclerosis (7 cases) autopsies.

Pulmonary findings in the autopsied patients were pneumonia in 25 (only 10 died of respiratory failure), pleuritis in 12, pulmonary hemorrhage in 6 (in 3 of them it was the direct cause death), cor pulmonale in 4, tuberculosis in 2 and pulmonary emboli in 1 patient.

The central nervous system autopsy findings were: cerebral edema in 4, cerebral vasculitis in 3, intracranial hemorrhage in 3, meningitis in 2 and cerebral herniation, hydrocephalus, and transverse myelitis in 1 autopsy each. The gastrointestinal findings in these autopsies were pancreatitis in 3 patients, chronic active hepatitis in 2, cirrhosis in 2, duodenal and gastric ulcers in 2, (both died from massive GI bleeding) and peritonitis in 1 patient.

Discussion

This data reveals that the most common cause of death is infection, as has been reported in the literature by Rosner et al (8) and others. All the fatal pneumonias were caused by pathogens in which cell-mediated immunity is the primary form of protection from infection. Even though in SLE there is a primary defect in cell-mediated immunity, the chronic use of steroids is the principal mechanism that results in a profound suppression of cell mediated immunity. Renal disease was the second most common cause of death, in agreement with the published data (9,10). The 15-year cumulative survival rate in patients without renal disease was 94%, very similar to other studies that demonstrated a greater-than-90% survival rate at 10 years (11). In that study, the 15-year cumulative survival rate for patients with renal disease was 64% thus, renal disease is a major mortality risk factor in patients with SLE. However, the results showed that the mortality due to uremia decreased as the years went by, a phenomenon probably due to an earlier diagnosis and the introduction of chemotherapeutic agents. Cyclophosphamide has been used in our hospital since 1984 and azathioprine since 1971.

The autopsies confirmed the clinical diagnosis. Most autopsies were done before 1975, where technological aids like echocardiography, CT scan, and MRI were not available. Unexpectedly, 37 autopsies (65%) revealed cardiac involvement, even greater than renal involvement (35 autopsies, 61%). As expected, CNS changes were not specific or unique, consisting mostly of cerebral edema and cerebral vasculitis. Even though the literature

frequently mentions the increased risk of malignancy in SLE, particularly non-Hodgkin's lymphoma (12), only one fatal malignancy (gastric adenocarcinoma) was reported in the autopsies.

One hundred nine patients (68%) died within 5 years of diagnosis. A previous study showed that the main causes of death early after the diagnosis of SLE (first 5 years) were infection and active SLE (13). Our study showed that mortality rates were higher in earlier decades; before 1975, the mortality rate was 32.4% and it decreased to 12.8% in the 1975-1994 period. In a similar fashion, the overall 15-year cumulative rate has increased from 72% prior to 1980 to 92% after 1980. This improvement in survival is probably related to earlier diagnosis of the disease, treatment with steroids and immunosuppressive agents (cyclophosphamide and azathioprine), better antibiotic treatment, and closer follow-up of the disease.

Since infection and renal disease are the leading causes of death from SLE, physicians need to be aware of their early signs and symptoms and institute early aggressive therapy in order to decrease the mortality of this disease.

Resumen

No existe información publicada acerca de la mortalidad de pacientes con lupus sistémico eritematoso (LSE) en Puerto Rico. En la literatura médica norteamericana se informa una mortalidad mayor en los pacientes con LSE de raza afro-americana y puertorriqueña residentes en los Estados Unidos que en población anglosajona. El propósito de este estudio es determinar las causas de muerte en la población de pacientes puertorriqueños con LSE que eran referidos a la clínica de Reumatología del Hospital Universitario. La información se recopiló retrospectivamente usando los expedientes médicos de 662 pacientes. Se encontró que 24% de todos los pacientes evaluados entre 1960 y 1994 murieron. La razón de sobrevida acumulada a 15 años fue de 76.6% pero en pacientes con enfermedad renal bajó a 64%. Las causas más frecuentes de muerte en los pacientes de LSE fueron las infecciones y las enfermedades renales; coincidiendo con lo publicado en la literatura médica.

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