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Analysis of Auto Antibodies, Mortality and Epidemiology of Hospitalized Patients for Systemic Sclerosis in a University Hospital

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Abstract

Introduction: Systemic sclerosis (SSc) is a chronic autoimmune disease of the connective tissue marked by fibrosis, which can have different clinical forms and variations in the number of cases between populations. **Objective:** Analyze the clinical and epidemiological characteristics of patients, the profile of autoantibodies and mortality from SSc at the Universitary Hospital of Teresina, PI, Brazil. **Methods:** Review of electronic medical records, with results presented in tables of absolute and relative frequencies. The association measures were expressed in estimated values of Odds Ratio (OR). For statistical significance, $p < 0.05$ was considered. **Results:** The profile found was predominantly of brown women, over 40 years old, with an average evolution of 6 years of illness, although there was a high percentage of men in the study. Mortality was high, with a significant association with male gender, age over 60 years, age at diagnosis over 60 years, patients from the interior of the state, hospitalization for pulmonary site infection and hospitalization over 30 days. The presence of the anti-centromere autoantibody (ACA) was 30.8%, associated with limited disease and pulmonary hypertension. Antitopoisomerase I antibody (ATA) predominated in patients with diffuse cutaneous fibrosis, interstitial pneumopathy and dysphagia, with a high percentage positivity (66.7%). **Conclusion:** The patient profile found follows Brazilian and international data. Mortality was high, with a greater number of early deaths and infectious causes. The prevalence of anti-Slc-70 was higher than the national average, but the profiles of involvement corroborate the pattern of autoantibodies described in the literature.

Subject Areas

Rheumatology

Keywords

Systemic Sclerosis, Autoimmunity, Scleroderma

1. Introduction

Systemic sclerosis (SSc) is a chronic autoimmune connective tissue disease that is often characterized by cutaneous sclerosis, the presence of autoantibodies in the patient's serum and vasculopathy. However, its pathogenesis is not fully understood and individuals may present clinical presentations of fibrosis to different extents [1].

Classically, it is subdivided into limited cutaneous forms, which present cutaneous damage only distal to the elbows and knees and above the clavicles, and diffuse, with extensive cutaneous fibrosis and a greater possibility of involvement of other organs, such as the heart, lungs, gastrointestinal tract and kidneys [1] [2].

In epidemiological studies of SSc, diversified results are observed in neighboring regions or in the same country. In Brazil, there are isolated studies on the prevalence and incidence of SSc, limited to a few cities [3] [4] [5]. However, there is still no national database on carriers of the disease.

The dosage of autoantibodies is important to determine the prognosis, especially for those with high specificity for SSc. Antitopoisomerase (ATA) stands out, predominant in diffuse disease, and anticentromere (ACA), is more characteristic of the limited cutaneous form [6], although the prevalence of autoantibodies may vary between populations. The simultaneous presence of ACA and ATA is rare, with a prevalence of 0.6% among SSc patients [7].

It is a disease whose related factors are not yet elucidated, suggesting the possibility of influence of environmental and/or ethnic aspects, due to the variation in the number of cases in the analyzed regions. Furthermore, it has different forms of presentation and different degrees of involvement, which sometimes delays the diagnosis and may underestimate the total number of cases. In this context, the objective of the study was to analyze the clinical-epidemiological characteristics of patients, the profile of autoantibodies and mortality from systemic sclerosis at the Universitary Hospital, Teresina, Piauí.

2. Methodology

2.1. Study Characteristics and Sampling

This is a cross-sectional and descriptive observational study, with data of a retrospective nature and a quantitative approach. The study was carried out at the University Hospital of the Federal University of Piauí (HU-UFPI), Teresina, Piauí.

The study population consisted of all patients with systemic sclerosis admitted to the Internal Medicine Unit (Rheumatology) from January 2014 to December

2019. The sample was complete, and non-probabilistic, in which the entire population was included in the study.

2.2. Inclusion and Exclusion Criteria

Patients over 18 years of age with a confirmed diagnosis of systemic sclerosis, according to the criteria of the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) [8] were included in the study.

Patients with overlapping rheumatologic diseases or scleroderma-like syndromes were excluded from the study. Multiple admissions of the same patient for similar reasons were considered only once.

Data were obtained from the electronic medical records of patients who met the inclusion criteria, by searching for the International Code of Diseases 10 (ICD10 M34 Systemic Sclerosis) at the Process Management and Information Technology Sector (SGPTI/HU-UFPI).

A structured form was then filled out in order to investigate sociodemographic and clinical variables, hospitalization data, presence of autoantibodies related to the disease and medication use.

The results are presented in tables of absolute and relative frequencies, calculating the mean and standard deviation in case of continuous variables. The association measures are expressed in estimated Odds Ratio (OR) values, with their 95% confidence interval (95%CI) and the p-value obtained. For statistical significance, $p < 0.05$ was considered.

3. Results

In total, 91 patients were found, of which 57 met the inclusion criteria. Females accounted for 77.2% of the participants and the female:male ratio was 3.4:1. The average age of the sample, the epidemiological characteristics and the hospitalization data are shown in **Table 1**. Individuals with a diagnosis time of up to 05 years (59.7%), coming from the interior of the state, with low education and who already performed prior outpatient follow-up at the service.

Twelve patients had two or more hospitalizations for different reasons and were fully accounted for in the research. Thus, there were 70 hospitalizations during the period considered, the main reasons being pulse therapy (44.3%) and the presence of infectious complications, especially pulmonary focus (57.1% of the total infections).

The most prevalent comorbidities found in the study patients were arterial hypertension (28.1%), osteoporosis (17.5%), diabetes mellitus and smoking (14.0% each), dyslipidemia (12.3%) and hypothyroidism (8.8%).

Eight hospitalizations resulted in deaths, which corresponds to 14.0% of the total sample. There were five deaths among male participants and 75.0% of deaths were due to infection of a pulmonary focus. The mean length of hospital stay until this outcome was 22.6 ± 22.9 days. There was a significant association between mortality and the variables described in **Table 2** ($p < 0.05$).

Table 1. Epidemiological characteristics and data of hospitalization in a group of patients with systemic sclerosis.

Variables	n(%)
Sex	
Male	13 (22.8)
Female	44 (77.2)
Age	49.5 ±11.4 years
Age at diagnosis	43.1 ± 13.0 years
Diagnosis time	6.4 ±6.2 years
Procedence	
Capital (Teresina)	18 (31.6)
Others cities of Piaui	25 (43.9)
Others states	14 (24.5)
Race	
Caucasian	05 (8.8)
Non Caucasian	52 (91.2)
Cause of Hospitalization	
Diagnostic tests	05 (7.1)
Follow-up exams	10 (14.2)
Pulse therapy	31 (44.3)
Infectious complication	14 (20.0)
Complication of the Disease	
Sclerodermic renal crisis	02 (2.9)
Others	02 (2.9)

Table 2. Factors associated with mortality in a group of patients with systemic sclerosis.

Variables	OR ($CI_{95\%}$)	P
Male	08.5 (1.7 - 43.1)	0.0094
Age > 60 years	08.8 (1.7 - 46.6)	0.0105
Diagnosis after age 60	28.8 (2.5 - 331.6)	0.0070
Patients from other cities in the state	31.6 (1.7 - 580.0)	0.0201
Hospitalization for pulmonary site infection	90.0 (10.7 - 758.9)	<0.0001
Hospitalization > 30 days	20.3 (1.6 - 258.5)	0.0202

OR (IC95%)—Odds Ratio (Confidence interval 95%).

Table 3 shows the symptoms and clinical findings identified, in order of prevalence, with sclerodactyly and Raynaud's phenomenon being the most frequent alterations. The presence of telangiectasias was also investigated, but was not recorded. Patients with skin thickening were subdivided according to the body areas of involvement described.

Regarding autoantibodies, 13 patients had an anticentromere antibody (ACA) result, 69.2% of which were negative. The result of antitopoisomerase antibody (ATA) was reported for 21 participants, 66.7% of which were positive, with a mean value of 229.5 ± 51.8. Antinuclear factor (ANA) was reported in 37 patients (91.9% positive), with a mixed pattern (nuclear and nucleolar) appearing in 39.3% of the available tests and a predominance of high titers (Table 4).

Among the patients who were positive for ACA and recorded data, 50.0% had the limited cutaneous form of SSc and 25.0% had pulmonary hypertension. Considering the antitopoisomerase antibody reagent, the diffuse cutaneous form was highlighted in 71.4% of the patients, the presence of dysphagia (64.3%) and dyspnea due to interstitial lung disease (57.1%).

The drugs prescribed for the treatment of SSc are shown in Table 5. Thirty-one patients (54.4%) underwent pulse therapy with cyclophosphamide on at least one occasion. Medication, doses and target organ are also described.

Table 3. Clinical findings in a group of patients with systemic sclerosis.

Signs/Symptoms	N	%
Sclerodactyly	42	73.7
Raynaud's phenomenon	33	57.9
Digital ulcers	27	47.4
Dyspnea	27	47.4
Dysphagia	26	45.6
Arthralgies	08	14.0
Leukomelanoderma	02	3.5
Calcinosis	02	3.5
Skin thickening		
Face	16	28.0
Cervical region	05	8.8
Upper limbs (proximal)	12	21.1
Chest	08	14.0
Abdomen	07	12.3
Lower limbs	07	12.3

Table 4. Results of autoantibodies in a group of patients with systemic sclerosis.

Autoantibodies	N	%
Anticentromero reagent	04	7.0
Antitopoisomerase reagent	14	24.6
Antinuclear factor (ana) reagent	34	59.6
Pattern		
mixed (nuclear + nucleolar)	11	19.3
nucleolar	07	12.3
centromerico	05	8.8
fine dotted nuclear	03	5.3
thick dotted nuclear	02	3.5
Titration		
1:80	01	1.8
1:160	04	7.0
1:320	05	8.8
1:640	11	19.3
1:1280 +	07	12.3

Table 5. Medications used by a group of patients with systemic sclerosis.

Medications	N	%
PPI	50	87.7
CCBs	43	75.4
Corticosteroids	32	56.1
Domperidone	22	38.6
Ace inhibitors	11	19.3
Methotrexate	11	19.3
Azathioprine	07	12.3
Mycophenolate mofetil	02	03.5
Cyclophosphamide	31	54.4
Target Organs		
Skin	12	21.1
Lung	19	33.3
Dose		
up 600 mg	02	03.5
800 mg	03	5.3
1000 mg	26	45.6
Totaldoses		
<12	14	24.6
12	14	24.6
>12	03	05.3

4. Discussion

The contribution of this study lies in the analysis of a population not considered in the reports of patients with systemic sclerosis (SS), a pathology still little addressed in Brazilian registries. Among the main findings, similarities in sociodemographic characteristics, different clinical profiles related to autoantibodies and factors associated with mortality with national and international data stand out, but there are also particularities regarding the participants considered to complement the investigation.

The study consisted mostly of women (female:male ratio 3.4:1), as observed in studies of SSc and other rheumatological diseases typically associated with females, although the total number of men was a high percentage in this study. National studies showed a ratio ranging from 7.7:1 to 28.6:1 [3] [4] [5]. In this respect, the finding was closer to the data from the populations of the United Kingdom and Taiwan (4.9:1 and 3.5:1, respectively) [9] [10].

The average age of patients at diagnosis corroborates data from the literature, which have the diagnosis already well established, mostly between the fourth and fifth decades of life [11] [12] [13] [14]. The time of disease verified, even if only the period after the definitive diagnosis is considered, characterizes the typical chronic course of the pathology [11].

Although Brazilian studies of SSc show a predominance of the white population [4] [5], the majority of patients in this study declared themselves to be non caucasian. However, a cultural miscegenation typical of Brazil and the Northeast region is important in the analysis of the data. Furthermore, the European Research Group on Sclerosis (EUSTAR) did not find between SSc cases and ethnicity for regions as in a multicenter study [15].

Most patients have low education and come from the interior of the state. Although the literature does not show an observation of the relationship between SSc and cultural and socioeconomic habits [9] [16] the research was developed in a health agreement hospital) and rheumatology care in Piauí is still quite centralized, that the health services of the capital responsible for much of the specialized care in the region, including patients coming from others.

Composing the main reason for the hospitalizations evaluated, pulse therapy with high doses of immunosuppressive medications is periodically indicated to reduce the speed of progression of the disease and control the symptoms [17], thus justifying the predominance of shorter hospitalizations. However, 20.0% of hospitalizations were due to infectious complications, probably as a result of immunosuppression, which compromises the immune response, especially pulmonary site infection, which accounted for 75.0% of total deaths.

Two patients were hospitalized for Sclerodermal Renal Crisis (SRC), a rare and severe acute kidney injury condition associated with SSc. It is usually related to the diffuse form of SSc, use of corticosteroids, chronic kidney disease and rapid progression of cutaneous fibrosis [18]. Mortality from SRC is still high—a French multicenter study observed 40% of deaths [19], but early treatment with

Angiotensin Converting Enzyme (ACE) inhibitors brought advances in reducing SRC mortality, corroborating its effectiveness in preventing mortality from this cause also in our sample.

The total mortality in the research was high—14.0% of the participants, especially considering that it is a cross-sectional study, with a short period analyzed. However, studies with access to long-term data also showed high rates, with mortality ranging from 17.7% to 31.8% [4] [9] [20]. The reduction in survival was associated with longer disease duration [9]. A European cohort had a mortality rate of 20.0% after a 9-year follow-up, with most deaths due to SSc complications, especially pulmonary involvement [11], whereas our study showed a predominance of early deaths and deaths from infectious causes.

In agreement with the data in the literature, the research shows a positive association of mortality with the male sex [4] [9] [11], since the pattern of many rheumatological diseases is predominantly female. Men may have more severe forms of SSc, although less frequent, due to factors not yet fully elucidated, but the influence of the hormonal profile is considered [4].

Elderly individuals who were diagnosed after the age of 60 had a higher mortality in this sample, possibly due to the comorbidities that traditionally affect this age group and worsen the patient's prognosis. However, there is also the possibility that the diagnosis was late, since SSc is typically of slow progression and, without specialized care, may not be identified for a long period [11]. Patients from the interior of the state, with difficult access to health services, also had high mortality in this study, possibly due to the lack of early diagnosis and adequate treatment.

Higher chances of death were also observed in patients hospitalized for pulmonary site infection and with hospitalization for more than 30 days. Presumably due to the immunosuppression condition, the patient frequently acquires opportunistic infections, requiring a long period of hospitalization, which in itself increases the risk of contagion by hospital-based multidrug-resistant pathogens [9].

Elombila *et al.* [21] carried out a study in Brazzavile evaluating deaths of patients in a multipurpose intensive care unit and they concluded that reducing the mortality rate would require, among other things, the implementation of morbi-mortality review meetings, the improvement of the technical platform, the availability of emergency products, and an increase in the number of medical staff.

We found a high mortality rate, the main cause being pulmonary infection, which shows that physicians should be aware of infectious conditions in patients with systemic sclerosis.

The predominant clinical signs of the disease in our patients were sclerodactyly and Raynaud's phenomenon (RyRP). The latter is considered the earliest sign in most patients and may appear, in isolation, years before [22]. However, other frequent signs, such as leukomelanoderma and telangectasia, were poorly

described or not included in the records, while the proportion of patients reporting dyspnea and dysphagia, symptoms of more severe or advanced disease, was high. Although it is important to consider that this is a hospital population, with a more severe condition, it is difficult to identify the earliest cutaneous signs in primary care, which contributes to late diagnosis.

With regard to autoantibodies, the reduced number of patients who performed the measurements stands out, especially of the autoantibodies with the highest association with the evaluated disease, that is, anticentromere (ACA) and antitopoisomerase (ATA). This reflects the difficulty of patients' access to these tests, which are expensive and have an irregular supply in health services, including the tertiary hospital considered. In addition, records can be made inadequately or incompletely, which certainly compromises data analysis.

Among the patients who underwent the dosage, high ANA titers were observed in a large proportion (91.9%), similar to the national data found in a study with patients with SSc followed up in an outpatient setting in Paraná (92.9%) [5]. A Uruguayan study showed ANA positivity in 79.6% of patients [13]. Although ANA does not provide a specific analysis for SSc, the presence of characteristic patterns aids in the investigation and rules out other diagnoses [23].

In parallel, ACA and ATA positivity rates were 30.8% and 66.7%, respectively. The existing Brazilian studies that seek to correlate the profile of autoantibodies and the manifestations of SSc also did not have a large sample, but obtained lower values of prevalence of anti-Scl-70. Two cross-sectional studies showed a predominance of ACA, with rates of 52.2% and 33.3%, and anti-Slc-70 positivity in 32.6% and 17.8% of participants, respectively [24]. Another research group from Paraná, which analyzed 85 patients, found a higher prevalence of ATA (31.76%) in relation to ACA (30.59%), but still lower than that found in our study [5].

Although it is estimated that 30% of individuals who have a positive ACA will not develop SSc [25], it is associated with the presence of the limited cutaneous form and pulmonary hypertension in SSc patients [24] [25] [26], in accordance with the results obtained in this study, in addition to intestinal hypomotility [5]. The presence of ACA is associated with a longer interval between the onset of RP and the development of other symptoms [25].

On the other hand, antitopoisomerase carriers are more predisposed to severe skin involvement, development of digital ulcers and interstitial lung disease (ILD) [5] [24] [25] [26]. They are also associated with increased renal vascular damage, CRE, fibrosis of the gastrointestinal tract and heart muscle [27]. In our study, it was associated with a higher prevalence of dysphagia, ILD and extensive cutaneous fibrosis, but there was no association of its presence with mortality. Patients with anti-Scl-70 who have a limited cutaneous form are at risk equivalent to the diffuse form of developing pulmonary fibrosis [6].

However, it is important to consider that this work covers a population that

has greater impairment when compared to patients who do not need hospitalization for the control of SS. This aspect may influence the high percentage of anti-Scl-70 observed, which has a worse prognosis, and, even in patients with only ACA positivity, the high prevalence of visceral manifestations or more difficult to control.

The treatment of SSc is based on the control of symptoms and the adoption of immunosuppressive and/or immunomodulatory therapy to delay the progression of the disease [17]. Patients with RPy benefit from the use of dihydropyridine calcium channel blockers (CCBs), such as nifedipine, as they reduce the amount and severity of ischemic attacks [22]. Thirty-three patients (57.9%) had RF identified, but 75.4% used BCC, which may suggest preventive use in hypertensive patients or a gap in the identification and recording of this change.

The European League Against Rheumatism (EULAR) endorses the use of methotrexate (MTX) for progressive skin involvement in the early stages of the disease [17]. However, there is no evidence that MTX is effective for visceral involvement. Although cyclophosphamide is usually reserved for patients with ILD from SSc, several studies have also reported improvements in skin involvement [13] [22]. A double-blind, randomized, placebo-compared study using daily oral cyclophosphamide in 158 patients, with response to IPD as the primary outcome, showed significant improvement ($p < 0.01$) in skin scores after 12 and 24 months of treatment [28].

In this research, a small proportion of patients using MTX is observed, while there is a similar number who undergo pulse therapy with cyclophosphamide for the skin, which may suggest that many have lung disease that contraindicates the use of MTX, have more aggressive skin disease or drug refractoriness. Patients with skin conditions with good response to MTX usually maintain outpatient follow-up without the need for hospitalization [22].

Patients using cyclophosphamide present significant improvement in the skin, oral opening and lung capacity, being effective in preventing fibrosis and its complications [29]. A European multicenter cohort showed a difference in forced vital capacity (FVC) of 2.5% and protection against fibrosis-associated FVC decline compared to placebo ($p < 0.03$ and $p < 0.009$, respectively), maintained across two years of the study, after minimal therapy with six months of cyclophosphamide [28]. Patients with more aggressive diseases, whether pulmonary or cutaneous, are more frequently referred to the University Hospital, which explains the high number of patients who receive CCF in their treatment.

5. Conclusions

Patients were mainly female, with a mean age of 49.57 years. The main complaints were sclerodactyly, Raynaud's phenomenon and the most frequently found antibody was the antitopoisomerase (ATA). Mortality was significantly associated with male gender, age over 60 years, age at diagnosis over 60 years, hospitalization for pulmonary site infection and hospitalization for more than 30 days.

The profile of the patients studied follows Brazilian and international data, although there is a high proportion of men in the study and the prevalence of antitopoisomerase was higher than the national average.

Conflicts of Interest

The authors declare no conflicts of interest.

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