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MALIGNANCIES AND THEIR EFFECTS ON DISEASE COURSE IN PATIENTS WITH SYSTEMIC SCLEROSIS

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Abstract

Objectives: Systemic sclerosis (SSc) is an inflammatory disease. Systemic inflammatory diseases increase the risk of malignancy. Malignancy prevalence has been reported previously as 3.6-10.7% in SSc. Standardized incidence ratios (SIRs) were calculated for lung cancer (4.9), skin cancer (4.2), hepatocellular carcinoma (3.3), hematological malignancies (2.3), esophageal cancer (15.9), and oropharyngeal carcinoma (9.6). Thus, the aim of this study was to document the prevalence of malignancies and their potential effect on disease course in patients with SSc with a 10-year follow-up.

Material and Methods: SSc patients from two territory hospitals diagnosed between 2010 and 2020 were included in the study. Demographical, clinical, and laboratory features were recorded. Cancer types and their effect on the features of SS were analyzed using suitable statistical methods.

Results: Five (3.4%) of 149 SSc patients (137 females and 12 males) had a cancer diagnosis, and their mean age was 54±6.4 years. All five were females, and the mean age of cancer diagnosis was 50±6.6 years. Two of them had breast cancer, one had ovarian cancer, one had soft tissue sarcoma, and the last one had basal cell carcinoma. Time to cancer diagnosis from SSc diagnosis was 6.6±5.5 (minimum-maximum: 2-14) years. Two of them died during the follow-up period. Three of SSc with concomitant cancer were diffuse cutaneous SSc and two cases were limited cutaneous SSc subtype. Only one patient had received cyclophosphamide treatment. Dysphagia and gastroesophageal reflux disease (GERD) are prevalent in patients with cancer.

Conclusion: This study shows that 3.4% of SSc patients have cancer risk. Dysphagia and other GERD symptoms are more prevalent in patients with concomitant cancer than in those without. Dysphagia and other GERD symptoms may be candidate surrogate markers of malignancy in patients with SSc.

Keywords: Scleroderma, sytemicsclerosis, malignancies, dysphagia, GERD

INTRODUCTION

Systemic sclerosis (SSc) is a chronic, multisystemic, autoimmune disease characterized by fibrosis of the skin and internal organs. It leads to changes in the skin, musculoskeletal system, lungs, heart, gastrointestinal system, and kidneys due to inflammation and fibrosis. The pathogenesis of SSc is thought to comprise a triad of abnormal autoimmune responses, small vessel vasculopathy, and increased fibrosis in tissues (1).

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Malignancies are an important part of the burden of comorbidities associated with rheumatic diseases (2). Increased cancer risk is associated with both basic immunological dysfunction and drug therapies. With the increase in effective treatments for SSc, mortality rates due to interstitial lung disease, pulmonary hypertension (PHT), and renal crisis are decreasing, whereas long follow-up periods increase the incidence of malignancy. Malignancy in SSc is frequently observed in patients with severe skin involvement and with anti-RNA polymerase III antibodies, one of the specific autoantibodies (3,4).

There are various rates in the literature regarding the prevalence of malignancy in patients with SSc (3.6-10.7%) (5). In a meta-analysis, the standardized incidence ratio (SIR) for all malignancies in patients with SSc was found to be 1.41 (6). It was observed that male patients had a higher SIR than female patients. However, contrary to what is known, there was no difference between the diffuse and limited types. In this meta-analysis, significant increases in the risk of lung, liver, and bladder cancers, non-Hodgkin's lymphoma, and leukemia were also observed. The increased risk for specific malignancies included lung cancer (SIR 4.9), skin cancer (SIR 4.2), hepatocellular carcinoma (SIR 3.3), hematological malignancies (SIR 2.3), esophageal carcinoma (SIR 15.9), and oropharyngeal carcinoma (SIR 9.6) (7,8).

In the literature, data on malignancy rates, malignancy types, and risk factors in patients with SSc are contradictory (9). Therefore, the aim of this study was to document the prevalence of malignancies in patients with SSc and their potential impact on the disease course with a 10-year follow-up.

MATERIAL AND METHODS

Before starting the study approval was obtained from the Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Committee (approval number: 774, date: 29/05/2021). Between 2010 and 2020, patients with SSc diagnosed with International Classification of Diseases diagnosis code who applied to two centers were screened and identified. The SSc diagnoses of the patients were confirmed according to the "2013 The American College of Rheumatology (ACR)/The European Alliance of Associations for Rheumatology (EULAR) SSc classification criteria". Patients who did not fulfill the 2013 classification criteria according to their file records were excluded from the study. Patients were screened for malignancy diagnosis through the hospital information management systems of the two centers, follow-up files, "e-Nabız" of the patients (it is an application where health professionals can access health data collected from health institutions over the internet), and the Medulla doctor system. Patients diagnosed with malignancy at least 2 years after the diagnosis of SSc were included in the study. Patients without a diagnosis of malignancy were enrolled as the control group. Clinical characteristics were recorded from the patients' files, laboratory characteristics were recorded through the hospital systems, and computed tomography (CT) findings of patients with thoracic CT (interstitial lung disease or pleural effusion) and echocardiographic findings of patients with echocardiography were recorded. Interstitial lung disease and PHT were determined according to international definitions (10,11). Those with skin involvement on the proximal knee, elbow, and trunk were classified as having diffuse SSc. Other patients were classified as limited (12).

Statistical Analysis

All data were recorded and analyzed using Statistical Package for Social Sciences (SPSS) for Windows 25 software. The conformity of the variables to normal distribution was evaluated by the Kolmogorov-Smirnov and Shapiro-Wilk tests. The t-test was used for normally distributed data, and the Mann-Whitney U test was used for nonparametric data. Results are expressed as mean $\pm$ standard deviation for normally distributed data and median and minimum-maximum for non-normally distributed data. For categorical variables, results were presented as numbers and percentages. The chi-square test was used for categorical variables between proportions. p-values 0.05 were considered statistically significant.

RESULTS

According to 2013 ACR/EULAR SSc classification criteria, 149 patients with SSc (137 F/12 M) were identified. Of the patients, 45 had diffuse SSc, 89 had limited SSc, and 9 had sine scleroderma.

Malignancy was detected in 5 patients (3.36%). The mean age of the patients with malignancy was 54$\pm$6.4 years. All 5 patients were female. The mean age at diagnosis of malignancy was calculated as 50$\pm$6.6 years. Invasive ductal breast cancer was diagnosed in 2 patients, basal cell carcinoma of the skin in 1, ovarian adenocarcinoma in 1, and soft tissue sarcoma in 1. The interval between the diagnosis of SSc and malignancy was a minimum of 2 years and a maximum of 14 years (6.6$\pm$5.5). Two of the patients died. One was malignancy-related, and the other was due to other accompanying medical problems.

Three of the patients were followed up with a diagnosis of diffuse SSc and 2 with a diagnosis of limited SSc. Impairment in pulmonary function tests was detected in 2 patients, interstitial lung disease was detected in 3 patients on CT, and PHT was detected in 2 patients on echocardiography. One patient

had received pulse cyclophosphamide treatment, 2 patients had received rituximab treatment, 3 patients had received methotrexate treatment, 2 patients had received azathioprine treatment, and one patient had received D-penicillamine treatment.

When SSc patients with and without malignancy were compared, patients with malignancy had older age (54±6.4 vs. 50.3±14.2 and longer follow-up period (10.60±4.8 vs. 8.3±5.5), but no statistically significant difference was observed (p=0.43 and p=0.24, respectively). The proportion of patients with diffuse SSc was higher in the malignancy group, but not statistically significant (60% vs. 11% p=0.36). Dysphagia and gastroesophageal reflux disease (GERD) symptoms were significantly higher in patients with a diagnosis of malignancy (p=0.048 and p=0.038). Platelet count was found to be statistically significant in patients with malignancy (p=0.06), close to the significance level. No significant difference was observed in terms of other clinical and laboratory characteristics (Table 1 and 2).

The rate of malignancy development in diffuse and limited SSc patients was calculated as 6.3% in diffuse SSc patients and 2.1% in limited SSc patients [p=0.34, odds ratio=2.97 (0.48, 18.40)] (Figure 1).

DISCUSSION

The risk of malignancy is increased in systemic autoimmune rheumatic diseases. Although this increased risk has not been fully elucidated, it is thought to be the result of both the effects of chronic inflammation and tissue damage caused by autoimmunity on cancer risk and the inadequacy of drugs used for treating rheumatic diseases and impaired immunity against oncogenic viral infections (13).

Although there are different data in the literature regarding the risk of malignancy development in patients with SSc, the general opinion is that the rate of malignancy increases. The estimated SIR range from 1.5 to 5.1 compared with the general population (2). The malignancies with the highest reported increased risk are lung cancer and non-Hodgkin's lymphoma (8,14). An increased risk of oropharyngeal and esophageal cancer has also been reported in patients with scleroderma (14). In a review by Wooten (5), data from 5686 SSc patients were pooled and 358 (6.3%) malignancies were reported (based on data from 7 studies with malignancy rates ranging from 3.6% to 10.7%). The most commonly reported malignancies were pulmonary, breast, and gastrointestinal. The malignancy rate in our study was lower than that reported in these studies (3.4%). Lung cancer, the most commonly reported malignancy, was not observed in our patients. Breast cancer, which is the second most common malignancy, was detected in 2 of our patients.

Olesen et al. (15) showed that the risk of developing malignancy was approximately 1.5 times higher in patients with SSc than in the general population according to data obtained from patients diagnosed with SSc from 1977 to 2006 in the Danish

Table 1. The demographical and clinical features of SSc with cancers and without cancer

Mean ± SD or percent	Malignant (n=5)	Non-malignant (n=144)	p
Sex (females), n (%)	5 (100)	132 (91)	1
Mean age, years	54±6.4	50.3±14.2	0.43
Follow-up period, years	10.6±4.8	8.3±5.5	0.24
Death, %	2 (40)	17 (11)	0.24
Diffuse cutaneous SSc, n (%)	3 (60)	45 (31)	0.36
Digital ulcer, n (%)	1 (20)	53 (37)	0.75
Pitting scar, n (%)	3 (60)	61 (42)	0.75
Telangiectasia, n (%)	2 (40)	20 (14)	0.33
Dysphagia, n (%)	**4 (80)**	**47 (32)**	**0.048**
GERD symptoms, n (%)	**4 (80)**	**44 (30)**	**0.038**
Dyspnea, n (%)	4 (80)	97 (67)	0.93
HRCT abnormalities, n (%)	3 (60)	63 (44)	0.35
FVC %	82±23.1	76±18.6	0.64
PAP, mmHg‡	28±8.4	28±15.5	0.57

Statistically significant values are shown in bold, ‡PAP values were recorded by echocardiography, SSc: Systemic sclerosis, SD: Standard deviation, GERD: Gastroesophageal reflux disease, HRCT: High resolution computerized tomography, FVC: Forced vital capacity, PAP: Pulmonary artery pressure

Table 2. The laboratory features and medications of SSc with cancers and without cancer

Mean ± SD or percent	Malignant (n=5)	Non-malignant (n=144)	p
Hemoglobin, g/dL	13.2±0.9	12.7±1.5	0.53
Leukocyte, $10^3/mm^3$	6.4±1.8	8.4±2.9	0.11
Platelet, $10^3/mm^3$	238±37.8	295.5±96.7	0.06
ESR, mm/h	23±20	23±17	0.90
CRP, mg/dL	0.5±0.4	1.1±3.1	0.61
Creatinine, mg/dL	0.6±0.1	0.6±0.2	0.56
ANA positives, n (%)	4 (80)	118 (87)	0.93
Anti-Scl70 positives, n (%)	1 (20)	51 (39)	0.64
Anti-centromere positives, n (%)	0	29 (22)	0.58
Anti-Ro positives, n (%)	2 (40)	25 (19)	0.56
Cyclophosphamide, n (%)	1 (20)	43 (29)	1
Rituximab, n (%)	2 (40)	12 (8.3)	0.1
Mycophenolate mofetil, n (%)	1 (20)	19 (13)	0.51
Methotrexate, n (%)	3 (60)	39 (27)	0.27
Azathioprine, n (%)	2 (40)	78 (54)	0.86
D-penicillamine, n (%)	1 (20)	2 (1.4)	0.09

SSc: Systemic sclerosis, SD: Standard deviation, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, ANA: Anti-nuclear antibody

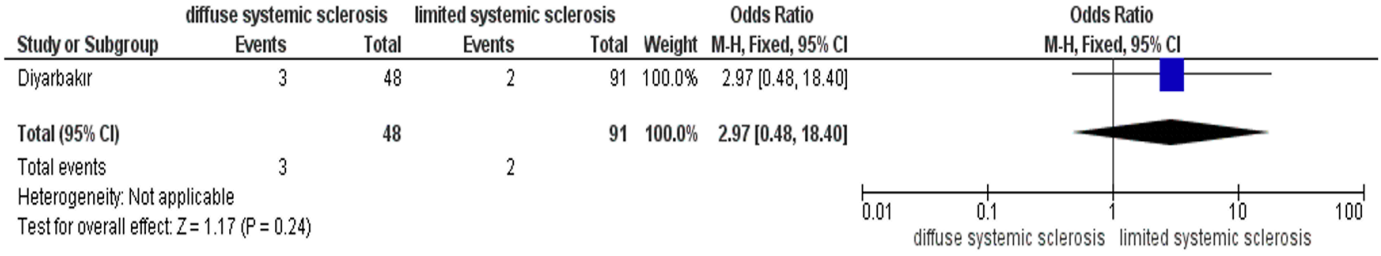

Figure 1. Malignancy risk ratio in patients with diffuse and limited SSc

national patient registry. In this study, the incidence of cancer was higher in men than in women (SIR 2.2 and 1.3, respectively). In general, male patients have a higher risk of malignancy (6). Only one review reported that older women have a higher risk of malignancy (5). In our study, all patients with malignancy were female, which may be due to the small number of male patients diagnosed with SSc.

Anti-RNA polymerase III SSc is associated with renal crisis (16). However, many studies have also found an association between anti-RNA polymerase III, an antibody specific for the diagnosis of SSc, and malignancy (4,17,18). Nikpour et al. (17) found that anti-RNA polymerase III antibodies were particularly associated with malignancy diagnosed within 5 years of the onset of SSc skin disease (13.3% vs. 3.9% in antibody positive patients). It was also found that these patients had a severe disease profile. In the study by Moinzadeh et al. (4), 2177 patients were screened and 7.1% had a history of cancer. When the autoantibody profile was evaluated, the prevalence of malignancy was calculated as 14.2% in anti-RNA polymerase III-positive patients, 6.3% in anti-Scl-70 antibody-positive patients, and 6.8% in anti-centromer antibody-positive patients, and the difference was significantly higher (4).

The occurrence of malignancy in rheumatological patients increases the burden of disease and negatively affects quality of life and life expectancy. It has been shown that 55% of deaths in SSc patients are directly related to SSc and 41% to non-SSc causes. The causes of non-SSc-related deaths based on the EUSTAR database are infections (13% of all deaths), neoplasia (13% of all deaths), and cardiovascular disease (12% of all deaths) (19). In

our study, the mortality rate was higher in patients diagnosed with malignancy (40% vs. 11%).

In a multicenter study conducted by Kaşifoğlu et al. (20) in which malignancy risk factors were evaluated in patients with SSc, 340 patients with SSc were screened and 25 patients (7%) were diagnosed with malignancy. 4 patients were diagnosed with bladder cancer, three with breast cancer, three with non-small-cell lung cancer, and three with hematological malignancy. When the data of patients with malignancy were compared with those of patients without malignancy, no statistically significant difference was found in demographic characteristics, organ involvement, autoimmune serology, cyclophosphamide use, and dose. However, higher doses of cyclophosphamide were used in patients with bladder cancer. In our study, GERD and dysphagia symptoms were reported more frequently in patients with malignancy. However, no significant difference was observed between the treatment options. In fact, we found that rituximab and mycophenolate mofetil, which are relatively safe, were preferred more in patients with malignancy. This is because malignancy patients have more aggressive disease. Cyclophosphamide, which is most commonly associated with the development of malignancy, was used in only one patient. This may be due to the clinician's anticipation of the risk of malignancy. In addition, we found that penicillamine treatment (although not widely used today) was used at a higher rate in patients with malignancy, although not statistically significant.

In another study by Sargin et al. (21) 153 patients were screened, and malignancy was detected in 7 patients. Malignancy was detected in three males and four females, and the mean age was 51.2 years. One lung cancer, 2 gastrointestinal system cancers, one myelodysplastic syndrome, two malignant melanomas (eye and skin), and one ovarian cancer were detected. Smoking, male gender, being diagnosed with diffuse SSc, and anti-Scl-70 positivity were reported as risk factors. In our study, we found a higher rate of malignancy in patients with diffuse SSc (6.3% vs. 2.1%). The odds ratio was calculated as 2.97 for the diffuse subtype.

Our study had some limitations. The number of patients with malignancy was low. Because the number of male SSc patients was low, we did not have a male patient diagnosed with malignancy. Risk factors could not be evaluated because our study was conducted through a retrospective file review. Our study included malignancies observed in a 10-year follow-up. In addition, the RNA polymerase III antibody, which was evaluated as a risk factor in most studies, was not evaluated in our patients.

CONCLUSION

The risk of cancer is increased in patients with SSc compared with the general population. It is important to perform age/gender appropriate malignancy screening in every case of clinical suspicion for early diagnosis and treatment in terms of a possible accompanying malignancy. However, routine screening of all patients is not recommended. Studies with larger case series are needed to determine malignancy screening recommendations and risk factors specific to SSc patients.

Ethics

Ethics Committee Approval: The study approval was obtained from the Diyarbakır Gazi Yaşargil Training and Research Hospital Ethics Committee (approval number: 774, date: 29/05/2021).

Informed Consent: A study retrospective was designed.

Authorship Contributions

Surgical and Medical Practices: İ.G., M.A.B., L.A., R.Ç., Concept: İ.G., M.A.B., L.A., R.Ç., Design: İ.G., M.A.B., L.A., R.Ç., Data Collection or Processing: İ.G., M.A.B., Analysis or Interpretation: İ.G., R.Ç., Literature Search: İ.G., L.A., Writing: İ.G.

Conflict of Interest: The authors have no conflicts of interest to declare.

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