Malignancy in scleroderma patients from south west England: a population-based cohort study

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MALIGNANCY IN SCLERODERMA PATIENTS FROM SOUTH WEST ENGLAND: A POPULATION-BASED COHORT STUDY

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ABSTRACT

BACKGROUND: The pathophysiological relationship between scleroderma and malignancy remains poorly understood. Although some previous studies have demonstrated an increased malignancy risk in patients with scleroderma, others have been inconclusive. We aimed to determine if patients with scleroderma had an increased risk of malignancy compared to an age and sex matched local South West England population, and if there were any important differences between scleroderma patients with and without malignancy. **METHODS**: Notes were obtained on all local scleroderma patients (n=68) locally, and those diagnosed with malignancy verified by contacting each patient's general practitioner. Expected malignancy figures were obtained from age- and sex stratified regional prevalence data provided by the South West Cancer Intelligence Service registry. **RESULTS**: 22.1% of patients with scleroderma were identified with concurrent malignancy. Affected sites were of the breast (n=5), haematological system (n=5), skin (n=4), and unknown primary (n=1). Overall, malignancy risk was found to be increased in scleroderma (RR 3.15, 95% CI 1.77–5.20, p=0.01). In particular this risk was highest for haematological malignancies (RR=18.5, 95% CI 6–43, p=0.05), especially for non-Hodgkin's lymphoma (RR=25.8, 95% CI 5–75, p=0.10). The majority of patients (86.7%) developed malignancy after the onset of scleroderma (mean=6.9years). Age of >70 and patients with limited scleroderma were significant risk factors for a patient with scleroderma to have a concurrent malignancy, however no increased risk was found in patients with any particular pattern of organ involvement, cytotoxic usage or serology. **CONCLUSIONS**: In this small patient cohort, we have found that scleroderma is associated with an increased risk of malignancy. This risk is statistically significant in patients with limited scleroderma. Patients who are elderly and those with limited disease should be closely scrutinized at follow-up appointments.

BACKGROUND

Whilst the association between certain site-specific malignancies and connective tissue diseases such as dermatomyositis,[1] polymyositis,[1] Sjogren's syndrome,[2] systemic lupus erythematosus,[3] and rheumatoid arthritis have become increasingly recognised over the years,[4] the association with scleroderma (systemic sclerosis) is less clear. This association was first proposed by Zatuchni in 1953,[5] who described alveolar cell carcinoma in a non-smoker with scleroderma. Since then, associations with tumours predominantly affecting the lung, breast and haematological systems have been most frequently reported.[6,7] Several cohort studies have been performed to explore this risk.[8-10] The first influential study consisting of 233 Swedish patients from Rosenthal *et al* discovered a relative risk of 2.5 for all malignancies, especially for lung, skin and haematological cancers.[7] Similar findings were reiterated by Hill *et al* in 2003.[8] Generally, studies have noted high concurrence rates ranging between 2.6% and 19%, and standardised incidence ratios (SIRs), i.e. ratio of observed malignancies to that expected, varying from 1.5 to 5.1.[7,8] However, from one of the largest studies from Detroit involving 538 patients, Chatterjee in 2005 found no increase in risk.[9] To our knowledge, no such study based within the United Kingdom had previously been performed. As such, the risk and pathophysiological relationship between scleroderma and malignancy within our population is still unclear.

Aims and Objectives

We aimed to determine if scleroderma patients within our local South West England population had an increased risk of malignancy and whether there were any identifiable predictors of malignancy.

Methods

We identified all patients with a diagnosis of scleroderma within a local South West English population of Bristol from a pre-existing scleroderma database encompassing a population of approximately 550,000. Patients were ascertained by scanning through coding databases of each regional healthcare trust for patients with scleroderma ICD codes who were affiliated with the Bristol region, e.g. for treatment, follow-up and referrals to other specialists. Patients who were known to be deceased at the time of the audit or those with

incomplete case notes were excluded from the study. Patients with malignancy were verified by contacting each patient's general practitioner. Case notes were scrutinised for key features including age, sex, scleroderma subtype, duration of illness, malignancy type, autoantibody profile and use of disease modifying anti-rheumatic drugs (DMARDs). Patients were classified into three categories: 'diffuse', 'limited' and 'overlap'. Patients were excluded if the diagnosis was unclear. Scleroderma categorisation was based on specialist diagnosis, and where unavailable, aided by demarcating parameters devised by LeRoy *et al.*[11] Scleroderma onset was defined as the earliest symptoms of proximal cutaneous sclerosis, and malignancy onset as the initial onset of symptoms. Malignancy prevalence rates from our follow-up period were compared with expected malignancy figures obtained from age and sex stratified regional prevalence data provided by the South West Cancer Intelligence Service registry. Patients with carcinoma *in situ* or without tissue diagnosis were not included in the analysis. Comparative analysis was performed using a web-based statistical package (Simple Interactive Statistical Analysis).[12] 95% confidence intervals (CIs) for relative risks (RRs) were approximated using the Poisson distribution, with two-tailed p-values calculated using paired student *t*-test. Fisher's exact test with two-tailed *p*-values was used for hypothesis testing wherever integers were available for comparison between two data subsets. Results were regarded as statistically significant when $p \leq 0.05$, and of borderline significance when $0.05 < p \leq 0.10$.

Results

We identified 68 patients with scleroderma. The study population consisted of 58 females and 10 males, with a median age of 57.5 years (S.D: 3.6, range: 17 to 86). 48 patients were classified under 'limited' (70.6%) and 12 under 'diffuse' (17.6%). 8 patients were classified under 'overlap' (11.8%) due to additional elements of systemic lupus erythematosus (*n*=3), mixed connective tissue disease (*n*=2), polymyositis (*n*=1), dermatomyositis (*n*=1) and rheumatoid arthritis (*n*=1).

In total, 15 malignancies were identified in 15 patients. Malignancies were seen in 25% of the diffuse group, 22.9% of the limited group and 12.5% of the overlap group. The overall concurrence rate of scleroderma and

malignancy from our study population was 22.1% (95% CI 14.1% to 35.4%). The observed cancer sites were of the breast (5), haematological system (5), and skin (4) and an adenocarcinoma of unknown primary (ACUP) [Figure 1]. Of the haematological malignancies, there were 2 patients with myeloma and 3 with non-Hodgkin lymphomas (NHLs), which consisted of diffuse large B-cell lymphoma, solitary IgM plasmacytoma, and mucosa-associated lymphoid tissue lymphoma of the thyroid.

Within our malignancy subgroup, the mean age of scleroderma diagnosis was 49.1yrs (SD=14.2). In 86.7% of patients (*n*=13), malignancy was diagnosed after the onset of scleroderma (mean=6.9 years). 2 patients with breast cancer and malignant melanoma were diagnosed prior to the onset of scleroderma. We found no significant correlation between malignancy type and the onset between scleroderma and malignancy. Demographic, clinical and serological comparisons conducted between the malignancy and control groups are summarised in Table 2. Patients with unknown data for any of the listed fields were omitted from analysis. Old age (>70 years) was a statistically significant risk factor for acquiring scleroderma-associated malignancy (*p*=0.02). No significant differences were seen between the two groups in terms of organ involvement, autoantibody profiles and DMARD use.

Age and sex-adjusted RRs for developing malignancies are summarised in Figure 4. The overall relative risk for developing malignant neoplasms was 3.15 (95% C.I. 1.77 to 5.20) and was considered statistically significant (*p*=0.01). This figure was high despite accommodating for malignancies with high prevalences within the general population that were not seen within our small cohort, for example: lung, gastrointestinal and gynaecological cancers. Consistent with previous literature, there was a statistically significant increase in occurrence of haematological malignancies associated with scleroderma (RR=18.51, 95% C.I. 6.01 to 43.19, *p*=0.03).

The malignant potential according to scleroderma subtype has also been explored. Previous studies have consistently demonstrated higher risks of malignancy in patients with diffuse scleroderma in comparison to

limited scleroderma and other forms of the disease.[8] From our cohort, the relative risk of malignancy in patients with diffuse scleroderma was 3.54, which was greater than that observed in limited scleroderma (RR 3.13) and other forms of the disease (RR=2.52). Due to the small number of patients with diffuse scleroderma and other forms of the disease, these risks did not achieve statistical significance (p=0.2 and p=0.6 respectively). However, in a sufficiently sized group of 48 patients with limited scleroderma, the relative risk of 2.52 for concurrent malignancy was significant (p=0.03).

DISCUSSION

Our results coincide with those from Duncan and Winkelmann's 1979 landmark study which reported breast and haematological malignancies as the most prevalent scleroderma-associated malignancies.[10] A Danish study by Jacobsen *et al* reported malignancy as the primary cause of death in 19% of scleroderma patients, where cancers of the lung (43%), haematological system (13%) and breast (10%) were predominantly implicated.[13] After excluding lung malignancies which were not observed in our study, these observations relate to the most frequently affected sites of malignancy as observed within our scleroderma cohort. Malignancies are thus important as they constitute a major cause of morbidity and mortality in scleroderma patients.

Despite our relatively small cohort, we did demonstrate a positive correlation between scleroderma and malignancy which was statistically significant. However, several other limitations within our study require acknowledgement. This was a retrospective, cross-sectional analysis of current patients with scleroderma without applying a strict observation interval. Statistical analysis comprised of comparing standardised prevalence rates instead of standardised incidence ratios. The observation that a positive smoking history was significantly less within the malignancy group (p=0.02) may suggest bias in data collection, however, this may have been accountable for the absence of lung cancer cases seen in the cohort. The relative risk of malignancy in our cohort was generally higher than previously reported. Although this may be explained by the high

prevalence of haematological malignancies within our cohort, it is possible that, due to a small sample size, small increases in malignancy cases can lead to disproportionate increases in relative risk. Furthermore, we speculate that if there had been more patients, *p*-values for risks ascertained from subgroup analysis, e.g. by sex and scleroderma subgroup, may have become significant.

The pathophysiology behind the potential association between scleroderma and malignancy is unclear, although we postulate that this involves dysregulation of molecular signalling pathways at an intracellular level. Of particular interest is the role of transforming growth factor-β (TGF-β), a ubiquitous profibrotic cytokine involved in the regulation of connective tissue proteins which is heavily overexpressed in sclerodermatous tissue. Dysregulated signalling of the TGF-β and downstream SMAD pathways have been demonstrated to induce tumorigenesis,[14] and has been implicated in malignancies seen within our cohort, i.e. breast, skin and haematological malignancies.[14,15] Furthermore, it is recognised that malignant transformation may be a sequela of chronic tissue damage. This mechanism has traditionally been implicated in the aetiogenesis of lung cancers in scleroderma due to associated pulmonary fibrosis, but may also be responsible for the development of cutaneous malignancies seen within our cohort. Interestingly, there were no patients with lung malignancies despite its reported frequency within the literature. We believe that this is partly due to the combination of low numbers of smokers and small numbers of patients with diffuse scleroderma which is typically associated with pulmonary involvement.

The use of DMARDs in the management of scleroderma has been implicated as a potential contributory factor towards the development of malignancy. Cyclophosphamide has been linked with a 30-fold increase in risk of bladder cancers, and an overall two to four-fold increase in haematological and skin malignancies.[17] Occasionally, malignancy may indirectly induce scleroderma as part of a paraneoplastic process. This has been observed in malignant carcinoid syndrome and also in POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes), which most commonly occurs in patients with IgA plasmacytoma.[18] Interestingly, one patient within our cohort developed skin changes consistent with limited scleroderma as part of POEMS syndrome and was eventually diagnosed with IgM plasmacytoma 2 months

later. In paraneoplastic scleroderma, processes driven by neoplasia are likely to be responsible. These processes have been postulated to involve abnormalities in antigen presentation, autoantibody genesis, disturbances of cellular immunity, cytokine imbalance, abnormal mediation of growth factors and hormones.[19]

CONCLUSION

From the first population-based analysis of scleroderma patients in South West England, we have found that the prevalence of malignancy is increased in scleroderma, particularly with haematological malignancies. Patients who are elderly and those with limited disease should thus be closely scrutinized at follow-up appointments.

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TABLES

Table 1: Demographic data of our study population.

	Overall	Men	Women
Number	68	**10** (14.7%)	**58** (85.3%)
Median Age	57.5	59.5	57
Scleroderma Type:			
a) Limited SSc	48 (70.6%)	6 (60%)	42 (72.4%)
b) Diffuse SSc	12 (17.6%)	3 (30%)	9 (15.5%)
c) Overlap	8 (11.8%)	1 (10%)	7 (12.1%)

Table 2: Comparisons between scleroderma patients with and without malignancy.

	Malignancy	Non-Malignancy	*p*-value	Overall
Female to Male ratio	14:1	4.9:1	0.439	5.8:1
Mean Age (S.D.)	63.5 (10.0)	56.8 (14.2)	0.046	58.3
Smoking History	13.3%	48.4%	0.021	37.0%
Articular involvement	70%	73.6%	1.000	73.0%
Pulmonary involvement	36.4%	48.1%	0.526	46.0%
CVS involvement	8.3%	19.2%	0.673	17.2%
Renal involvement	20%	20.8%	1.000	20.7%
Gastrointestinal involvement	75%	64.2%	0.737	64.6%
Neurological involvement	50%	24%	0.128	28.3%
Endocrine involvement	30.8%	17.3%	0.274	20%
ANA	50%	72.7%	0.257	68.5%
Scl-70	20%	29.7%	1.000	28.6%
ACA	28.6%	42.5%	0.685	38.3%
DMARD Use	40%	24.5%	0.326	29.8%

Table 3: Age and sex standardised relative risks of malignancy in scleroderma patients. O=Observed, E=Expected. ╫Denotes all malignancies registered into the South West Cancer Institute database, including those not observed within our cohort.

	O	***E***	**RR *(95% CI)***	***p-value***
Haematological	**5**	0.27	**18.51** (6.01 to 43.2)	0.03
a) NHL	**3**	0.11	**25.83** (5.32 to 75.5)	0.10
b) Myeloma	**2**	0.041	**49.08** (5.94 to 177)	0.17
Breast carcinoma	**5**	1.63	**3.07** (1.00 to 7.16)	0.18
Melanoma	**1**	0.23	**4.27** (0.11 to 23.8)	0.49
Basal cell carcinoma	**3**	0.58	**5.13** (1.06 to 15.0)	0.19
ALL Malignancies ╫	**15**	4.76	**3.15** (1.77 to 5.20)	0.01

Table 4: Age- and sex-standardised malignancy risks based on scleroderma subtype. Key: As per Table 3. *p<0.05

	Diffuse (*n*=12)			**Limited (*n*=48)**			**Overlap (*n*=8)**		
	O	***E***	**RR *(95% CI)***	***O***	***E***	**RR *(95% CI)***	***O***	***E***	**RR *(95% CI)***
Haematological	**0**	-	-	**4**	0.20	**20.13** (5.48 to 51.5)	**1**	0.023	**43.2** (1.09 to 241)
a) NHL	**0**	-	-	**2**	0.084	**23.68** (2.87 to 85.5)	**1**	0.010	**98.3** (2.49 to 547)
b) Myeloma	**0**	-	-	**2**	0.027	**73.95** (8.96 to 267)	**0**	-	-
Breast carcinoma	**1**	0.26	**5.36** (0.10 to 21.4)	**4**	1.22	**3.28** (0.89 to 8.40)	**0**	-	-
Melanoma	**0**	-	-	**1**	0.17	**5.92** (0.15 to 33.0)	**0**	-	-
Basal cell carcinoma	**1**	0.13	**7.64** (0.19 to 42.5)	**2**	0.51	**3.89** (0.47 to 14.1)	**0**	-	-
ALL Malignancies ╫	**3**	0.85	**3.54** (0.73 to 10.3)	**11**	3.51	**3.13** (1.56 to 5.61)*	**1**	0.40	**2.52** (0.06 to 14.0)

FIGURES

Figure 1: Malignancies within our scleroderma study sample.