HHS Public Access

Author manuscript

J Rheumatol. Author manuscript; available in PMC 2019 September 14.

Published in final edited form as:

J Rheumatol. 2005 April ; 32(4): 637–641.

Increased Incidence of Carcinoma of the Tongue in Patients with Systemic Sclerosis

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Abstract

Objective.—To describe the incidence of carcinoma of the tongue in a large cohort of patients with systemic sclerosis (SSc).

Methods.—In total, 769 patients with SSc were prospectively followed over 16 years for the development of cancer. Patients with a diagnosis of carcinoma of the tongue were identified to determine the incidence of this cancer in SSc. The results were compared to the incidence of tongue cancer in the SEER cancer registries.

Results.—A total of 3775 patient-years of followup of 769 patients with SSc (392 diffuse cutaneous, 377 limited cutaneous) prospectively evaluated for the occurrence of cancer disclosed 9 patients who were diagnosed with oral cavity and pharyngeal carcinomas. Six of these patients had squamous cell carcinoma of the tongue. One of these had both pharyngeal and tongue squamous cell carcinomas within a 4-year period, and another had 3 separate squamous cell carcinomas of the tongue. The standardized incidence ratio of squamous cell carcinoma of the tongue observed in this cohort of patients with SSc was 25-fold higher than that expected in an age adjusted population from the SEER cancer registries. All patients with SSc identified within this cohort with oral cavity carcinomas had the diffuse subset of the disease.

Conclusion.—There is a highly significant increase in the incidence of squamous cell carcinoma of the tongue in patients with SSc. A remarkable observation was that all patients within this cohort who developed oral cancer had the diffuse subset of SSc. This suggests a relationship between the etiology or pathogenesis of the diffuse form of SSc and development of squamous cell carcinoma of the tongue in this group of patients.

Keywords

SYSTEMIC SCLEROSIS; ORAL CAVITY CANCER; TONGUE CANCER; SQUAMOUS CELL CARCINOMA; TISSUE FIBROSIS

Numerous studies have examined the association of systemic sclerosis (SSc) and malignancies[1–6]. The majority of these studies, including a large population based study

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from the South Australian Scleroderma Registry, have shown an increased risk of cancer in patients with SSc[1–5]. In contrast, a study in a well characterized cohort of 490 patients with SSc from the Detroit Scleroderma Registry[6] showed no increased risk of cancer in patients with SSc. In 1987 we initiated a prospective study to assess the association of malignancies and SSc. During the course of this study we noted a remarkable number of SSc patients who had oral cavity malignancies, most being squamous cell carcinomas of the tongue. We describe this previously unrecognized association between squamous cell carcinoma of the tongue and SSc.

Squamous cell cancer of the tongue is a relatively rare malignancy in the developed countries, with roughly 7100 cases reported in 2003 in the United States compared with more common forms of cancer such as breast or lung with 212,600 and 185,800 cases, respectively, during the same period. Despite its relative rarity, tongue cancer is the second most common cancer of the oral cavity. The estimated yearly death rate from this cancer is about 1700 cases[7]. Several exogenous agents such as tobacco and heavy alcohol use as well as poor oral hygiene associated with dental and gum disease have been shown to increase the risk of oral cancer[8]. Viral oncogenes may also play a role in its occurrence. Human papilloma viruses 16 and 18 and the Epstein–Barr virus have been studied in patients with oral carcinomas; these studies have yielded contradictory results[9,10]. Certain cultural traditions may also influence the development of oral cancer. Areca catechu (betel nut) chewing has been linked to an epidemic of oral carcinoma in India and Asia. In these cases, a condition develops termed “submucous oral fibrosis,” a form of severe and progressive fibrosis of the oral cavity that bears histopathologic resemblance to the cutaneous fibrotic lesions of SSc, and in many cases it evolves into an oropharyngeal carcinoma[11].

During a longterm prospective evaluation of the occurrence of cancer in 769 patients with SSc followed at the Scleroderma Center of our institution during the last 16 years, 9 patients with squamous cell carcinoma of the oral cavity or pharynx were identified. Six of these patients had squamous cell carcinoma of the tongue. We describe here the clinical features and pertinent laboratory studies in these patients and demonstrate that there is a 25-fold increase in the frequency of carcinoma of the tongue in SSc patients compared to the general population. This observation raises the provocative possibility that both squamous cell carcinoma of the tongue and SSc may be caused by a common agent such as an orally ingested chemical substance or an infectious agent that enters the organism through the oral mucosa.

MATERIALS AND METHODS

In 1987 we initiated a prospective study to evaluate the association of cancer with SSc. The study was designed to test the hypothesis that there was an increased incidence of malignancy in patients with SSc, which was formulated based on the results of a retrospective analysis of SSc patients followed by one author (SAJ) at another institution during the period 1973–87[12,13]. The present study comprised a cohort of 769 patients diagnosed with either diffuse or limited SSc prospectively followed between 1987 and 2002 for the development of cancer at the Scleroderma Center of Thomas Jefferson University. All patients fulfilled the American College of Rheumatology criteria for classification of

SSc[14]. Each patient was questioned in detail for the occurrence of cancer at the initial visit as well as at each followup visit (every 3 to 6 months). Three hundred ninety-two (50.9%) patients had the diffuse cutaneous subset of SSc and 377 (49.1%) had the limited cutaneous subset. Following a report of the development of a malignancy by the patient, the diagnosis was confirmed through a comprehensive review of medical records, communications with referring physicians and with physicians who made the diagnosis and/or treated the cancer, and review of pathology reports. Basic demographic and clinical data for this population were recorded and certain possible risk factors for oral cancer were identified. The observation interval was defined by the entry date, which was the first recorded visit to our clinic, and the exit date, the last recorded visit to the clinic, and the patient-year of followup was calculated by subtracting these 2 dates.

Statistical analysis.

Quantitative data are presented as a mean with a 95% confidence interval, while qualitative data are presented as a percentage of the total. The expected numbers of oral and pharyngeal carcinomas, as well as tongue squamous cell carcinomas in the study population were calculated by multiplying the number of person-years at risk by an age adjusted population during the same calendar years from the SEER (Surveillance, Epidemiology and End Results Program) cancer registries[15]. The annual incidence rate for oropharyngeal and tongue cancer was multiplied by the number of patient-years of followup of the total SSc population to yield the expected cancer rates for the population studied. A standardized incidence ratio (SIR) was calculated from the ratio of observed to expected cases and a 95% confidence interval is given as described by Breslow and Day for Poisson parameters[16]. To calculate the SIR it is necessary to include the exact length of followup for the cohort (patient-years of followup), therefore, only the cases of cancer that had developed at least a year after the diagnosis of SSc and only the first diagnosed oropharyngeal cancer diagnosed in each patient were used for the final analysis of cancer rates. One patient developed 2 tongue cancers before study entry and SSc diagnosis, and a third tongue cancer after study entry, none of which were included in the final analysis for incidence. For completeness, the clinical description, demographics, and other relevant information are included for all patients who had oropharyngeal cancer and SSc.

RESULTS

The study population comprised 769 patients who were diagnosed with either limited or diffuse cutaneous SSc and were followed at the Scleroderma Center of Thomas Jefferson University over the past 16 years. Each patient was questioned in detail for the occurrence of any type of malignancy at the initial visit as well as at each followup visit. The average length of followup for this population was 4.9 ± 0.7 years, with a total followup of 3775 patient-years. From this population 9 (1.1%) patients were diagnosed with oral or pharyngeal carcinoma, 6 of whom (0.8%) had a diagnosis of squamous cell carcinoma of the tongue. One patient had 3 separate primary squamous cell cancers of the tongue. Two of these were diagnosed prior to the development of SSc. The remaining 5 patients were diagnosed with squamous cell carcinomas of the tongue at least one year after the diagnosis of SSc (Table 1). One patient developed an initial squamous cell cancer of the tongue and

then a subsequent pyriformis sinus squamous cell cancer. The mean age at SSc diagnosis for the group of 6 patients with SSc who had squamous cell carcinoma of the tongue was 49.2 ± 20.3 years and at cancer diagnosis 56.3 ± 11.1 years (Table 2). Fifty percent of these patients were men and 83% were Caucasian, not of East Indian descent. All patients with SSc and squamous cell carcinoma of the tongue had the diffuse form of the disease; 50% of patients received treatment with D-penicillamine, but none received antimetabolite or cytotoxic therapy such as methotrexate or cytoxan. Typical risk factors such as tobacco and alcohol use were present in only one of these patients, whereas family history for cancer was present in 33% of the patients (Table 2).

All patients had a positive test for antinuclear antibodies. The immunofluorescence pattern was speckled in 2 patients, nucleolar in 2, homogeneous in one, and not specified in 2. No patient was positive for either anti-Scl-70 or anticentromere antibodies. Assessment of visceral SSc involvement revealed that in all cases the disease was severe, with 4 patients displaying severe gastrointestinal symptoms including one patient with esophageal stricture, 3 with clinical and radiologic evidence of interstitial lung disease, one with severe pulmonary hypertension, and 2 who developed scleroderma renal crisis (Table 3).

A comparison of cancer rates in the SSc cohort with those of an age adjusted population from the SEER registries for carcinoma of the tongue and oropharyngeal carcinoma was performed. To be able to calculate the oropharyngeal cancer rate in our cohort, only cases that developed their first tongue cancer at least one year after diagnosis of scleroderma were included. The expected cases of cancer of the tongue and oropharynx for our population's patient-years of risk were 0.2 and 0.83, respectively, while the observed cases were 5 for tongue cancer and 8 for oropharyngeal cancer. This analysis revealed a 25-fold increase in the incidence of carcinoma of the tongue (95% CI 3.05–46.95) and a 9.63-fold increase of oropharyngeal carcinomas (95% CI 2.97–16.29) in the SSc population. All of the cancers observed were squamous cell carcinomas.

DISCUSSION

To our knowledge and from a detailed review of the English language literature, this is the first report of a case series describing an association between squamous cell carcinoma of the tongue and systemic sclerosis. Of interest is that only one of the patients in this series had exposure to typical risk factors for squamous cell carcinoma of the tongue, such as tobacco and alcohol use. An overall increase in cancer incidence has already been described in relation to SSc and, specifically, lung and breast carcinoma and squamous cell carcinoma of the skin[1–5]. This interrelationship has been further strengthened by studies showing protooncogene expression in peripheral blood T lymphocytes in patients with SSc[17], as well as defective cell apoptosis in these patients[18]. Potential causative agents for both cancer and SSc could be a viral infection or a chemical substance that enters the organism through the oral mucosa. Indeed, chemical exposure to vinyl chloride has been linked to the development of both cancer and SSc[19,20]. As for oral and pharyngeal cancer in patients with SSc, a provocative hypothesis could be formulated, which postulates that an environmental agent that gains access through the oral cavity is capable of causing either a malignancy or SSc or both depending on other associated factors such as, for example, the genetic

predisposition of the host. There is a well substantiated precedent that certain exogenous agents could be responsible for the occurrence of tissue fibrosis or a malignancy or both. For example, it has been well documented that certain individuals, most commonly of Asiatic origin, who have the habit of chewing betel nuts develop a type of oral fibrosis known as submucous oral fibrosis, which in many instances evolves into oral or pharyngeal cancer[11,21]. Another potential agent implicated in both the development of SSc and squamous cell carcinoma of the tongue is perchloroethylene, an organic solvent used in the dry cleaning industry and as a metal degreaser[22,23]. A third example is the remarkable epidemic of severe and progressive renal fibrosis in individuals who consumed herbal remedies containing aristolochic acid, many of whom subsequently developed various malignancies of the urinary tract[24,25].

Another plausible explanation for the association between SSc and squamous cell carcinoma of the tongue is that the presence of microstomia caused by the fibrotic process in the face leads to poor oral hygiene and gingivitis, which are considered risk factors for the development of oral and pharyngeal malignancies. This explanation, however, appears less likely from the series of patients reported here, since we found that all cases of oral and tongue carcinomas in our series occurred in patients with the diffuse form of SSc, although patients with the limited cutaneous subset of the disease often display more severe microstomia and for longer periods of time than those with the diffuse cutaneous subset.

Although our results clearly reveal an increase in the incidence of tongue and oral cavity squamous cell carcinomas in patients with SSc compared with the expected incidence of this malignancy in the United States, a recent population study from Australia failed to show such an association[5], as did other studies[1–4], and a more recent study published in abstract form analyzed the incidence of cancer in the Detroit Scleroderma Registry[6]. The reasons for the differences between our study and others are not readily apparent. One possibility is that the followup period in our cohort after the diagnosis of SSc was longer than in other studies, particularly for patients with the diffuse form of the disease. Other possibilities include ascertainment bias in our cohort, since the SSc patients referred to the tertiary SSc facility of our institution are often more severely affected and have more complicated disease. Indeed, if ascertainment bias was responsible for the inclusion of patients with oral or tongue cancer, the calculated SIR would be reduced substantially. However, that there were several cases of oral cavity/tongue cancers in our population of SSc patients remains unquestionable.

A limitation of our study is that it was not population based; our cohort included patients from various geographic regions of the United States and from other countries, and therefore cancer registries could not be used to directly compare the incidence of oral cancer in patients with SSc with that of the general population. However, we believe a comparison with the expected incidence obtained from data in the SEER database should provide a close approximation. Despite the limitations, this comparison showed a remarkable increase in the incidence of squamous cell carcinoma of the tongue in our cohort of SSc patients. As noted, this observation raises the hypothesis that an environmental agent acquired by the oral route may play a role in the development of both squamous cell carcinoma of the tongue and/or SSc. Further, the remarkable dissociation in the occurrence of tongue carcinoma between SSc patients with the diffuse and limited forms of the disease, with the exclusive occurrence

of this cancer in patients with diffuse SSc in this cohort, raises the possibility that both forms of SSc may have different etiology and/or pathogenesis, as discussed recently[26]. Further studies are needed to explore this hypothesis, which may provide valuable information about the etiology and pathogenesis of this disease.

Acknowledgments

Supported by National Institutes of Health grant AR19616 (Dr. Jimenez) and National Institutes of Health training grant AR07583 (Dr. Derk).

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Table 1.

Oral and pharyngeal cancer cases in a cohort of 769 SSc patients.

Oropharyngeal Carcinoma Sites	Pre-SSc Diagnosis	Post-SSc Diagnosis	Total
Squamous cell carcinoma of tongue	2	6	8*
Squamous cell carcinoma of pharynx	0	2	2
Pyriformis sinus squamous cell carcinoma	0	1	1**
Squamous cell carcinoma of tonsil	0	1	1
Total	2	10	12

*One patient had 3 separate primary squamous cell carcinomas of the tongue, 2 occurring before the diagnosis of SSc.

**One patient had both a squamous cell carcinoma of the pyriformis sinus and a squamous cell carcinoma of the tongue.

Table 2.

Demographic characteristics, risk factors, and treatment of patients with SSc and squamous cell carcinoma of the tongue.

Clinical Feature	Patients with SSc/Squamous Cell Carcinoma of the Tongue
Age at diagnosis of SSc, yrs	49.2 ± 20.3
Age at diagnosis of cancer, yrs	56.3 ± 11.1
Sex	50% male
Race	83% Caucasian; 17% African American
No. of patients	6
No. of cancers	8
Mean duration of followup, yrs	4.5
SSc clinical subset: diffuse/limited, %	100/0
Tobacco exposure, %	16.6
Alcohol exposure, %	16.6
Family history of cancer, %	33 (pancreatic cancer, head and neck squamous cell cancer)
D-penicillamine, %	50
Methotrexate, %	0
Cytoxan, %	0

Table 3.

Selected clinical features of SSc patients with squamous cell carcinoma of the tongue.

Clinical Feature	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age at diagnosis of tongue cancer, yrs	58	55	46	76	48	55,57,58*
Sex	M	F	F	M	M	F
Race	C	C	C	C	C	AA
Tobacco exposure	Yes	No	No	No	No	No
Alcohol exposure	Yes	No	No	No	No	No
ANA	Positive	Positive	Positive	Positive	Positive	Positive
ANA pattern	Speck	NA	Nucl/speck	NA	Homo	Nucl
ANA titer	640	NA	640	NA	> 640	320
Anti-Scl-70	Negative	Negative	Negative	Negative	Negative	Negative
Anticentromere	Negative	Negative	Negative	Negative	Negative	Negative
GI	Yes	NA	Yes	No	Yes	Yes
Lung	ILD	NA	No	No	ILD	ILD
Heart	No	NA	No	No	> PAH	No
Kidney	No	NA	SRC	SRC	No	No

C: Caucasian; ANA: antinuclear antibodies; speck: speckled; nucl: nucleolar; homo: homogeneous; GI: SSc related gastrointestinal involvement; Lung: SSc related pulmonary involvement; Heart: SSc related cardiac involvement; Kidney: SSc related renal involvement; ILD: interstitial lung disease; PAH: pulmonary artery hypertension; SRC: scleroderma renal crisis; NA: information not available.

*Patient had 3 separate carcinomas of the tongue.