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Concise report

Increased risk of papillary thyroid cancer in systemic sclerosis associated with autoimmune thyroiditis

Alessandro Antonelli[1], Clodoveo Ferri[2], Silvia Martina Ferrari[1], Andrea Di Domenicantonio[1], Dilia Giuggioli[2], David Galleri[3], Paolo Miccoli[3] and Poupak Fallahi[1]

Abstract

Objectives. Patients with SSc have an increased risk of malignancy compared with the general population. Before now, no study has evaluated the risk of thyroid cancer (TC) in SSc patients. The aim of the study was to evaluate the prevalence of TC in SSc patients.

Methods. We studied the prevalence of TC in 327 unselected SSc patients in comparison with two population-based, gender- and age-matched control groups (654 subjects from an iodine-deficient area and 654 subjects from an iodine-sufficient area). Thyroid status was assessed by measurement of circulating thyroid hormones and autoantibodies, thyroid ultrasonography and fine-needle aspiration cytology (when necessary).

Results. Circulating thyroid-stimulating hormone, anti-thyroglobulin and anti-thyroperoxidase antibody levels, and the prevalence of hypothyroidism were significantly higher in SSc patients ($P < 0.01$, for all). Six patients with papillary TC (PTC) were detected among SSc patients, whereas only one case was observed in each of controls 1 and 2 ($P = 0.007$, for both). In SSc all patients with TC had evidence of thyroid autoimmunity *vs* 40% of the other SSc patients ($P = 0.001$).

Conclusion. These data suggest a high prevalence of papillary TC in SSc patients, in particular in the presence of thyroid autoimmunity; careful thyroid monitoring would be opportune during the follow-up of these patients.

Key words: thyroid cancer, SSc, thyroid nodules, thyroid autoimmunity.

CLINICAL SCIENCE

Rheumatology key messages

- Papillary thyroid cancer is predominantly observed in SSc patients with respect to iodine-deficient and iodine-sufficient controls.
- All SSc patients with papillary thyroid cancer have thyroid autoimmunity, *vs* 40% of other SSc patients.
- A careful thyroid evaluation should be carried out during the follow-up of SSc patients.

Introduction

Patients with SSc may have an increased risk of malignancy compared with the general population [1]. A wide array of cancers has been reported in scleroderma, although lung and breast cancers are thought to be the most common [2].

Papillary thyroid cancer (PTC) presents most commonly between 30 and 50 years of age, with a preponderance of female/male = 3:1. Radiation exposure is a risk factor for PTC [3]. The prevalence of PTC is higher where iodine intake is excessive, or in case of iodine prophylaxis [4].

A longitudinal follow-up study has shown a high incidence of new cases of hypothyroidism and thyroid dysfunction in female sclerodermic patients, suggesting that the ones who are at high risk [those with a borderline high (even if in the normal range) thyroid-stimulating hormone

[1]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, [2]Department of Medical, Surgical, Maternal, Pediatric and Adult Sciences, University of Modena & Reggio Emilia, Modena and [3]Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Pisa, Italy

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Correspondence to: Alessandro Antonelli, Department of Clinical and Experimental Medicine, University of Pisa, Via Savi, 10, Pisa 56126, Italy. E-mail: alessandro.antonelli@med.unipi.it

(TSH) value, anti-thyroperoxidase antibody (AbTPO) positivity and a hypoechoic and small thyroid] should have periodic thyroid function follow-up [5].

A few studies have reported sporadic cases of PTC in patients with SSc [6, 7].

The present (case–control) study prospectively investigated prevalence and features of thyroid cancer (TC) in a large series of unselected patients with SSc in comparison with two matched samples from the general population with differing iodine intake.

Methods

Subjects

SSc patients

A total of 327 SSc patients consecutively referred to the Rheumatology Units of the University of Pisa and Modena (from 1995 to 2009) were recruited into the study. SSc was classified according to the ACR 1980 preliminary criteria [8]. Standardized criteria were followed for the evaluation of clinico-serological features, main visceral organ involvement and disease activity [9]. In SSc patients, disease duration ranged from 7 to 112 months; skin sclerosis was observed in all patients (diffuse 52% or limited 48%); visceral involvement included: peripheral vascular system, 94%; gastrointestinal system, 51%; lung, 64%; joint/tendons, 21%; heart, 35%; kidney, 9%. The prevalence of autoantibodies, evaluated according to standard methodologies [9], was: antinuclear 91% (with nucleolar pattern 24%), anti-centromere 37%, anti-topo I (anti-Scl-70) 41%.

Controls

Since iodine intake differs within Tuscany, and reliable data on local iodine intake based on urinary iodine excretion are available, two different control groups were used.

The first group consisted of controls from an iodine-deficient area. Among 3124 subjects randomly extracted from the general registry of North-West Tuscany and systematically screened for thyroid disorders, two individuals of same gender and similar age (± 5 years of age), for each SSc patient, were randomly selected and used as a population-based, gender- and age-matched control group (Table 1). The majority (87%) of these control subjects had resided in an iodine-deficient area for 20 years or more, which was considered a criterion of historical iodine deficiency.

The second group consisted of controls from an iodine-sufficient area. This control group was obtained choosing two individuals of same gender and similar age (± 5 years of age), for each SSc patient, who were randomly extracted from the background population of an area of iodine sufficiency (central Tuscany) who had been screened for thyroid disorders. Among these control subjects, 19% had resided in an iodine-deficient area for 20 years or more (Table 1). Control subjects with previous radiotherapy were excluded. All patients and controls gave informed consent for the study, which was approved by the Institutional Ethics Committee (Comitato Etico di Area Vasta Nord-Ovest).

All patients and controls underwent a complete clinical evaluation (Table 1) and were prospectively evaluated with respect to TSH, free thyroxine (FT4), free triiodothyronine (FT3), anti-thyroglobulin antibody (AbTg), AbTPO determination and physical examination, thyroid US, and fine-needle aspiration (FNA) (if necessary).

US of the neck and FNA

Neck US and FNA were performed as previously reported [3]. FNA was performed in palpable nodules; nodules that were not palpable were examined by FNA only when clinical findings or the echographic pattern [10, 11] suggested the opportunity of excluding malignancy (>8 mm, solid hypoechoic appearance, and/or irregular or blurred margins, and/or microcalcifications) [12].

Laboratory evaluation

Serum levels of TSH (DiaSorin, USA; reference range 0.3–3.6 mIU/l), FT3 and FT4 (AMERLEX-MAB FT3/FT4 Kit; Amersham, Little Chalfont, UK), AbTPO and AbTg (ICN Pharmaceuticals, USA; positivity was set at >100 kIU/l) were evaluated.

Statistical analysis

Data are expressed as mean (S.D.). For continuous variables, group differences were tested by analysis of variance; when this was significant at the $P \leqslant 0.05$ level, between-group comparisons were carried out by the Bonferroni–Dunn test. Group differences were tested for categorical variables, by Fisher's Exact test (two-tailed). Furthermore, the odds ratio was used when at least one case of thyroid disorder was observed in the controls. A $P < 0.05$ was considered significant. We used StatView software, Version 5.0, SAS Institute Inc., SAS Campus Drive, Cary NC 27513, USA, for statistical analysis.

Results

The samples had similar distributions by gender, age (by selection criteria) and smoking habits (Table 1). A positive family history of thyroid disease was significantly more frequent in controls from the iodine-deficient area and in SSc patients than in controls from the iodine-sufficient area.

In SSc patients, serum TSH levels, AbTg and AbTPO titres were significantly higher, whereas FT3 and FT4 were significantly lower in comparison with the other groups (Table 1).

Hypothyroidism (defined as a TSH level >4 mIU/l, in the presence of normal or low values of FT3 and/or FT4) was significantly more common in SSc patients than in the other groups. The prevalence of subclinical and clinical hyperthyroidism (defined as a TSH level <0.3 mIU/l, in the presence of normal or high values of FT3 and/or FT4) was not significantly higher in SSc patients (Table 1). Non-thyroidal illness syndrome [defined as low serum FT3, normal to low FT4, high reverse T3 (ranging from 1.08

TABLE 1 Clinical characteristics and comparison of thyroid status between patients with SSc and controls

Data	Controls (iodine deficient)	SSc	Controls (iodine sufficient)	P-value
n	654	327	654	
Age, mean (S.D.), years	55 (11)	54 (14)	54 (13)	0.724
Men/women, %	8/92	8/92	8/92	1
Iodine deficiency, %	87[a,d]	57[a,e,f]	19	<0.0001
Familial thyroid disease, %	46[a,d]	38[a,e]	18	<0.0001
Smokers, %	22	21	24	0.526
TSH, median (range), mIU/l	1.2 (0.01–8.7)	3.2 (0.01–51.4)[b,e,f]	1.4 (0.1–9.6)	0.0013
FT4, mean (S.D.), pmol/l	11.4 (3.1)	9.5 (5.1)[b,d,f]	12.2 (2.9)	0.537
FT3, mean (S.D.), pmol/l	5.1 (1.5)	4.6 (1.6)[b,d,f]	4.9 (2.1)	0.421
AbTg, median (range), kIU/l	31 (3–321)	135 (2–1213)[b,d,f]	47 (1–476)	0.041
AbTPO, median (range), kIU/l	29 (1–423)	115 (9–2132)[b,d,f]	28 (4–432)	0.0005
$AbTg^+$, %	8	18[b,d,f]	12	0.0001
$AbTPO^+$, %	7	35[b,d,f]	9	0.0001
Hypothyroidism, TSH >4 mIU/l, %	3	20[c,e,f]	5	<0.0001
Hyperthyroidism, TSH <0.3 mIU/l, %	3	4	2	0.172
Thyroid nodules, %	25 (163/491)	28 (91/236) 0.26 *vs* iod def	15 (98/556)[c,d]	<0.0001
Papillary thyroid cancer, n	1	6[e,f]	1	0.007

[a]$P < 0.05$ by χ^2. [b]$P \leqslant 0.05$ by the Bonferroni–Dunn test or Mann–Whitney U test (for TSH, AbTg, AbTPO). [c]$P < 0.05$ by χ^2, or by Fisher's Exact test. [d]Iodine deficient *vs* iodine sufficient. [e]SSc *vs* iodine sufficient. [f]SSc *vs* iodine deficient. AbTg: anti-thyroglobulin antibody; AbTPO: anti-thyroperoxidase antibody; FT3: free triiodothyronine; FT4: free thyroxine; TSH: thyroid-stimulating hormone; n: number.

to 2.46 nmol/l) and normal TSH] was observed in 3% of SSc patients.

The prevalence of thyroid nodules was higher in control subjects from the iodine-deficient area and in SSc patients than in the controls from the iodine-sufficient area (Table 1). FNA was performed in 14% of SSc patients [57 nodules in 46 patients were biopsied, 1.2 (mean) nodules biopsied (range 1–2) per patient receiving FNA; median nodule size was 19 mm], in 13% of iodine-deficient controls [108 nodules biopsied in 85 patients, 1.3 (mean) nodules biopsied (range 1–3) for each patient submitted to FNA; median nodule size, 21 mm] and 9% of iodine-sufficient controls [77 nodules biopsied in 59 patients, 1.3 (mean) nodules biopsied (range 1–2) per patient submitted to FNA; median nodule size, 18 mm].

Following standard criteria [13], the cytological samples were subdivided into classes: class 1, macrophages and colloid with no or rare follicular cells; class 2, benign nodule; class 3, indeterminate follicular lesion; class 4, suspect or frankly malignant. The distributions of cytological results in SSc, iodine-deficient and iodine-sufficient groups were: class 1 (7, 8, 8%, respectively); class 2 (82, 85, 86%, respectively); class 3 (4, 7, 8%, respectively). No significant differences in the distribution of classes 1, 2 and 3 results between the three groups were observed (χ^2, P = 0.9).

Four class 4 (7%) suspect or frankly malignant cytological results were observed in SSc patients. This class of results was only observed in the SSc group. Thyroidectomy was performed in all patients and controls with class 3 cytology; upon histological examination, a PTC was found in two SSc patients and in one subject from each control group. In the four SSc patients with class 4 cytology, post-thyroidectomy histological examination revealed PTC.

To sum up, six PTCs were detected in the SSc series, while only one case was observed in each control group (Table 1) [P = 0.007, by Fisher's Exact test (two-tailed) P-value, for SSc *vs* each control group]. The size of nodules with cancer, at histological examination, varied from 8 to 43 mm (median 19 mm). The TNM Classification of Malignant Tumours stage [14] was T1 in three, T2 in two and T3 in one of the PTC patients; no case of lymph node or distant metastasis was detected.

The ^{V600E}*BRAF* mutation was observed in one of the three patients evaluated. No other endocrine neoplasias were found in SSc patients.

The odds ratio for PTC was significantly higher in SSc patients than in iodine-sufficient controls (odds ratio = 12.2; 95% CI: 1.9, 77.4).

SSc patients with PTC did not differ from the other SSc patients (Table 2) in terms of gender distribution (M/F: 1/5, 27/294; respectively), age [54 (12), 55 (11), years; respectively], serum TSH [TSH in non-nodule-SSc, in benign-nodule-SSc and in PTC-SSc were, 3.5 (95% CI: 0.01, 51.4), 2.9 (95% CI: 0.01, 11.2) and 3.1 (95% CI: 0.4, 6.7), respectively; P = ns], FT3, FT4, AbTg or AbTPO concentrations. Five SSc patients with PTC had positive circulating thyroid autoantibodies (AbTg titre: 11, 28, 42, 191, 641, 823 kIU/l, respectively; AbTPO titre: 11, 109, 122, 218, 292, 713 kIU/l, respectively) at the time of surgery, and three had PTC in the context of chronic thyroiditis on histological examination. Altogether, all SSc patients with PTC had evidence of thyroid autoimmunity (6 *vs* 0), whereas only 40% (128 *vs* 193) (Fisher's Exact test P = 0.004) of SSc patients without TC exhibited

Table 2 Clinical and laboratory data in SSc patients with (CA-SSc) or without papillary thyroid cancer (SSc)

	SSc	CA-SSc	P-value
Total, n	321	6	
Age, mean (s.d.), years	55 (11)	54 (12)	0.675[a]
Men/women, n	27/294	1/5	0.418[b]
Diffuse/limited, n	168/153	2/4	0.432[b]
Anti-antinuclear Ab (±), n	293/28	5/1	0.429[b]
Anti-centromere Ab (±), n	119/202	2/4	>0.999[b]
Anti-topo I Ab(±), n	130/191	2/4	>0.999[b]
AbTg (±), n	59/262	3/3	0.084[b]
AbTPO (±), n	109/212	5/1	0.021[b]

[a]ANOVA; [b]Fishers's Exact test P-value. n: number.

evidence of thyroid autoimmunity (Table 2). The presence of PTC was not associated with any specific SSc treatment, or duration of the disease.

Discussion

This study is the first to show that PTC is observed with higher prevalence in SSc patients than in age- and gender-matched iodine-deficient controls, and iodine-sufficient controls. To eliminate bias in the observed prevalence of TC due to differences in iodine uptake, control groups from both high- and low-iodine-intake regions were used [4]. The results show a significantly higher prevalence of PTC in SSc patients than in either control group. The low prevalence of PTC in the control groups is in agreement with the low prevalence of TC (1/1411 subjects screened) recently reported from a population-based study in Southern Italy [10]. However, we cannot completely rule out that surveillance bias may be a possible explanation for finding more cancers in the cases than in controls undergoing routine screening.

The mechanisms connecting SSc and malignancies are unknown. The occurrence of different cancer types in association with SSc or SSc-like disorders suggests a range of underlying mechanisms, including altered immune response, common genetic and environmental links, disease-dependent factors, tumour-derived biologic substances and therapies [2]. The process of sclerosis itself may favour cancer in certain sites, such as lung and breast [2].

In our patients, autoimmune thyroid involvement and hypothyroidism were more frequently observed in patients with SSc than in the comparison groups, in agreement with results from other studies [15, 16]. An association between TC and chronic thyroiditis has been observed in many studies [17, 18].

In our study, features of thyroid autoimmunity were observed in all SSc patients with PTC, in comparison with its occurrence in 40% of SSc patients without TC, reinforcing the hypothesis that thyroid autoimmunity may be a predisposing condition for PTC. In our SSc patients, TSH was higher in the SSc group than in controls, and it is known that nodules are statistically more often malignant in patients with higher TSH [19]. Even though TSH levels in non-nodule-SSc, in benign-nodule-SSc and in PTC-SSc were not significantly different, we cannot exclude the possibility that a high TSH could be associated with PTC in SSc.

Another hypothesis proposed to explain the increase in cancers in SSc patients is the exposure to medications [2]. However, the presence of PTC was not associated with any specific treatment of SSc in our series. Furthermore, no specific treatment of SSc is known to be associated with TC.

Whether the B-Raf proto-oncogene, serine/threonine kinase (BRAF)-Mitogen-Activated Protein Kinase (MEK)-extracellular signal-regulated kinases (ERK) pathway activation plays a common role in PTC and SSc remains to be investigated; however, we have found the ^{V600E}*BRAF* mutation was observed in one among three patients evaluated, in line with the frequency observed in PTC patients without SSc [20].

In conclusion, this study is the first to show an increased risk of PTC in SSc patients, and an association with thyroid autoimmunity. As such, we recommend that careful thyroid evaluation (by US, FT4, TSH, AbTPO measurements) should be carried out during the follow-up of these patients.

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