Chronic lymphocytic thyroiditis: could it be influenced by a petrochemical complex? Data from a cytological study in South-Eastern Sicily

Salvatore Arena, Adele Latina¹, Roberto Baratta², Giuseppe Burgio³,
Damiano Gullo² and Salvatore Benvenga^{1,4,5}

A.S.P. 8 Siracusa, Department of Internal Medicine, Section of Endocrinology and Metabolic Diseases, Umberto I Hospital, Siracusa, Italy, ¹Department of Clinical and Experimental Medicine, University of Messina, Italy, ²Endocrinology Division, Department of Clinical and Molecular Biomedicine, University of Catania, Garibaldi-Nesima Hospital, Catania, Italy, ³A.R.P.A. Sicilia (Agenzia Regionale per la Protezione Ambientale) District of Siracusa, Italy, ⁴Master Program in Childhood, Adolescent and Women's Endocrine Health, University of Messina and ⁵Interdepartmental Program in Molecular and Clinical Endocrinology & Women's Endocrine Health, University Hospital of Messina, Messina

Correspondence
should be addressed
to S Arena
Email
salvoarena72@hotmail.com

Abstract

Introduction: In genetically predisposed individuals, exogenous factors (including pollution) influence the development of Hashimoto's thyroiditis/chronic lymphocytic thyroiditis (CLT). CLT may also be a risk factor for associated thyroid cancer. Few data are available on the role of pollution from petrochemical complexes, one of which is located in the Siracusa province (South-Eastern Sicily), in the pathogenesis of CLT.

Aims: i) To study the frequency of CLT in fine-needle aspiration cytology (FNAC)-interrogated thyroid nodules from patients who were stably resident in their zones, comparing it in patients living in the petrochemical complex area (zone A) with that of patients from a control area (zone B). ii) To study the frequency of CLT in the FNAC categories of malignancy risk, comparing the two zones.

Patients and methods: We retrospectively evaluated cytologically adequate slides of 1323 nodules in 1013 outpatients who underwent ultrasound-guided FNAC from 2006 to 2012. We stratified by area of residence, gender, and FNAC categories of malignancy risk.

Results: CLT was detected with significantly greater frequency in either patients or nodules from zone A compared with zone B (32.0% vs 23.1%, $P=0.002$ or 28.2% vs 18.8%, $P=0.0001$), with a female preponderance (F=35.2% vs M=21.1% or 30.4% vs 20.4%, zone A and F=26.5% vs 12.3% or 21.6% vs 9.5%, zone B). Regardless of zone, CLT was approximately twofold more frequent in the suspiciously malignant+malignant classes (TH4+THY5=47.6%, zone A and 32.4%, zone B) compared with the benign+intermediate classes (THY2+THY3=27.3%, zone A and 18.2%, zone B), but with a clear stepwise THY2 through THY5 increase only in zone A (THY2=25.3%, THY5=66.7%; THY2=18.6%, THY5=28.6% in zone B).

Conclusions: The petrochemical complex-related pollution is an environmental factor involved in the development of CLT and, likely, in the CLT association with thyroid neoplasms.

European Journal of
Endocrinology
(2015) 172, 383–389

Introduction

Chronic lymphocytic thyroiditis (CLT) or Hashimoto's thyroiditis (HT) has a prevalence of 1–4% and incidence of 3–6/100 000 population per year (1), and is the result of a combination of genetic (endogenous) and nongenetic

(exogenous) factors (2). Its incidence is rising, and pollution could be one reason for such increase (2, 3, 4, 5, 6).

In our previous studies (4, 5, 6), which were conducted in tertiary endocrine centers of the Universities of Messina

Clinical Study	S Arena and others	Chronic lymphocytic thyroiditis and pollution	172:4	384
----------------	--------------------	---	-------	-----

and Catania (the two main cities of Eastern Sicily), we reported that the frequency of HT has greatly increased over the years. At least for Messina, the data obtained at the endocrine division (based on functional, thyroid autoimmunity, and thyroid ultrasound (US) evidence) (4) were confirmed at the Cytology Unit from the same university hospital based on evidence of CLT from thyroid nodules that were interrogated by fine-needle aspiration cytology (FNAC) (5).

Based on the interest generated by these reports (4, 5, 6) and the existence of a large petrochemical complex in South-Eastern Sicily, located just 15 km north of the third main city of Eastern Sicily (Siracusa), we planned to investigate the possible role of environmental pollution in CLT. Siracusa lacks a university medical center, but an US-guided FNAC (US-FNAC) ambulatory exists in the Division of Internal Medicine. In brief, we compared the frequency of CLT in the FNACs performed on nodules of patients living in an area that hosts a large petrochemical complex and that spans three towns with that in a control area (Siracusa city) located 15 km south of that area. We also compared, in the two areas, the association of CLT with the category (or class) of the FNAC. To our knowledge, such FNAC-based study is unprecedented in the literature.

Patients and methods

We retrospectively evaluated consecutive diagnostically adequate cytological slides of 1323 nodules in 1013 outpatients who resided permanently in the areas of South-Eastern Sicily specified below, and who underwent US-FNAC that had been performed and read by the same operator (S Arena) at the Section of Endocrinology, Department of Internal Medicine, Umberto I Hospital of Siracusa, from 2006 to 2012. All smears were read in a blinded vision, and presence or absence of CLT was evaluated at the same time of the attribution of THY class of risk, and not performing another reading. Moreover, all CLT+ve cases were blinded reviewed by another operator (A Latina), and only in case of concordance, specimens were included in the study. At least two aspirations for each nodule were performed using a 23-gauge needle. Smears were prepared and stained with hematoxylin and eosin (Papanicolaou method).

Examined nodules were assigned to the appropriate THY class, and cytological features of CLT, when present, were based on the diffuse presence of lymphocytes in the background and/or infiltrating thyroid follicles with marked signs of phlogosis and moderate amounts of

colloid. Additional finding that could or could not be present were as follows: follicular atrophy, plasma cells, multinucleated giant cells, epithelioid cell clusters, intra-lobular fibrosis, and Hürtle-cell metaplasia. This metaplasia may display some chromatin clearing, nuclear atypia, nuclear grooves, and prominent nucleoli sometimes overlapping with malignant lesions (7, 8). Because inherent to the diagnostic purpose of FNAC, evaluated nodules have to be assigned to a cytological class (or category) of malignancy risk, the association of CLT with these classes was virtually automatic. We followed the classification of the British Thyroid Association/American Association of Clinical Endocrinologists/Associazione Medici Endocrinologi/European Thyroid Association (BTA/AACE/AME/ETA) (9, 10). This classification considers five categories, from THY1 (inadequate) to THY5 (malignant). Inadequate cases (THY1) were not included in the study.

Based on the rationale of our study, the 1013 patients were subdivided according to the area of their stable residence: zone A and zone B. Zone A referred to the towns of Augusta, Melilli, and Priolo, with a total population of 61 515 (36 075+13 322+12 218) inhabitants. The petrochemical complex, one of the largest refining industry in the world, occupies territory in those three towns, and is predominantly oriented to the production of medium-heavy crude oils with a high sulfur content in the distillates. Zone B (the control area), which is located ~15 km south of the southern border of zone A, is the city of Siracusa (118 644 inhabitants). Zone B is separated from zone A by a promontory (Climiti Hills; maximum height 410 m above the sea level), that could be considered as a 'protecting' barrier from pollutants produced by the industrial hub. The population in the study area is quite homogeneous in terms of ethnicity, food, alcohol consumption, iodine intake, and smoking habit. No age differences were found in the studied subjects (females: 54.5 ± 13.8 and $53. \pm 14.3$ years in zone A and 54.5 ± 12.7 years in zone B – males: 53.9 ± 13.9 and 53.4 ± 14.3 years in zone A and 54.2 ± 13.5 years in zone B).

Data from the Sicily Environmental Protection Agency (ARPA; Agenzia Regionale per la Protezione Ambientale, <http://www.arpa.sicilia.it/>), with nine pollution sensing stations in zone A and four in zone B, support that the two zones are 'environmentally distinct'. These data are based on the levels of heavy metals in the atmosphere of the two areas of study. Air quality evaluation was based on the measurement of the concentrations of fine particulate matter in the air and of various compounds in lichens, small vegetables originated from fungi and algae and able

to absorb substances from the atmosphere, that are considered as good indicators of environmental quality (11). For instance, concentration (in mg/kg of dry weight) of the following heavy metals was greater in zone A compared with area B: nickel (2.85 vs 0.31, $P=0.02$), vanadium (6.65 vs 1.39, $P=0.03$), chromium (1.98 vs 0.16, $P=0.12$), and mercury (0.06 vs 0.03, $P=0.13$).

Sample-size estimate and power

An *a priori* sample-size estimate was conducted on the basis of the ability to detect a difference in CLT prevalence between nodules from the two areas (zones A and B). To detect an outcome proportion of 28% in zone A and 19% in zone B with a relative group size of 35% in zone A and 65% in zone B at an acceptable error rate ($\alpha=5\%$ and $\beta=20\%$), the minimum sample size required was $n=280$ in zone A and $n=519$ in zone B (total study size, $n=799$).

Statistical analysis

Data are mean $\pm$ s.d. We compared proportions of categorical variables with the χ^2 -test and Fisher's exact test.

Multivariate logistic regression analysis was applied to assess the CLT prevalence in the two different areas independently of the other parameters tested. The dependent variable in this model was the binary status (absence=0 and presence=1) of CLT. The area of residence was the main independent predictor included as a categorical variable (zone B=0 and zone A=1). Other independent predictors included as categorical variables were gender (male=0 and female=1) and THY class (THY2+THY3=0 and THY4+THY5=1). The results are presented as adjusted odds ratios (ORs) with 95% CIs.

The significance limit was set at P values <0.05 . Data analyses were performed using Prism (GraphPad, San Diego, CA, USA) and SPSS (SPSS, Inc.) statistical packages.

Results

Because our cohort consists of patients with single or multiple thyroid nodules, results are given using two denominators (thyroid nodules and patients). In either way, data are presented in patients stratified based on zone of residence, with a further distinction based on gender.

Table 1 summarizes that of the 1013 total patients, 391 were from zone A and 622 from zone B. This 1.6-fold greater representation of zone B patients is in line with the 1.9-fold greater number of inhabitants (see above, 'Patients and methods' section). In terms of nodules, the fold difference was 1.7 (490 vs 833). Females and males had the same distributions in the two zones, with a F:M ratio of 3.3:1 both in zone A and zone B.

Prevalence of CLT

Overall, CLT was detected in 269 of the 1013 patients (26.6%) and 295 of the 1323 of the nodules (22.3%; Table 1). However, CLT was more frequent in zone A compared with zone B (32.0% vs 23.1% of patients, $P=0.002$ and 28.2% vs 18.8% of nodules, $P=0.0001$). This predominance in zone A compared with B held regardless of the singularity or plurality of the nodules (Table 2). In the single nodule group, rates were 30.5% (zone A) and 21.9% (zone B) of patients or nodules; in the multiple nodule group, rates were 36.4 and 25.6% of patients or 24.7 and 15.9% of nodules.

Table 1 Absolute and relative (%) distribution of chronic lymphocytic thyroiditis or nodules in patients in the two zones. Additional comparisons in per patients and per nodules modality.

Modality	Zone	Females	Males	Total (and female: male ratio)
Per patients	A	$n=301$	$n=90$	$n=391$ (3.3:1)
	CLT +ve	106 (35.2%)	19 (21.1%)	125 (5.6:1) (32.0%)
	B	$n=476$	$n=146$	$n=622$ (3.3:1)
	CLT +ve	126 (26.5%)	18 (12.3%)	144 (7.0:1) (23.1%)
Per nodules	Statistics A vs B	$\chi^2=6.73$, $P=0.01$	$\chi^2=3.25$, $P=0.07$	$\chi^2=9.57$, $P=0.002$
	A	$n=382$	$n=108$	$n=490$
	CLT +ve	116 (30.4%)	22 (20.4%)	138 (28.2%)
	B	$n=643$	$n=190$	$n=833$
	CLT +ve	139 (21.6%)	18 (9.5%)	157 (18.8%)
	Statistics A vs B	$\chi^2=9.82$, $P=0.002$	$\chi^2=7.04$, $P=0.008$	$\chi^2=15.45$, $P=0.0001$

Zone A, females vs males ($\chi^2=6.34$, $P=0.01$ and $\chi^2=4.16$, $P=0.04$); Zone B, females vs males ($\chi^2=12.56$, $P=0.0004$ and $\chi^2=14.14$, $P=0.0002$).

Clinical Study	S Arena and others	Chronic lymphocytic thyroiditis and pollution	172:4	386
----------------	--------------------	---	-------	-----

Table 2 Absolute and relative (%) distribution of chronic lymphocytic thyroiditis or nodules, based on single or multiple nodules, in patients in the two zones.

Modality	Zone	Single	Multiple
Per patients	A	n=292 89 (30.5%)	n=99 36 (36.4%)
	B	n=411 90 (21.9%)	n=211 54 (25.6%)
	Statistics A vs B	$\chi^2=6.62$, <i>P=0.01</i>	$\chi^2=3.79$, <i>P=0.05</i>
Per nodules	A	n=292 89 (30.5%)	n=198 49 (24.7%)
	B	n=411 90 (21.9%)	n=422 67 (15.9%)
	Statistics A vs B	$\chi^2=6.62$, <i>P=0.01</i>	$\chi^2=6.97$, <i>P=0.008</i>

P values typed in boldface italics are borderline significant (between 0.10 and 0.05).

In either zone, more females had CLT compared with males (zone A: 35.2% vs 21.1%, $P=0.01$ and zone B: 26.5% vs 12.3%, $P=0.0004$). This gender difference held expressing data per nodules (zone A: 30.4% vs 20.4%, $P=0.04$ and zone B: 21.6% vs 9.5%, $P=0.0002$; Table 1).

While patients (or nodules) had an identical gender representations in the two zones (3.3:1), this representation differed in the two areas, though insignificantly, upon considering the CLT-positive patients (zone A, 5.6:1 and zone B, 7.0:1) or nodules (zone A, 5.3:1 and zone B, 7.7:1), indicating that males in zone A were relatively more prone to develop CLT compared with males in zone B. Although F:M ratio was higher in zone B, even if correlation between females gender and autoimmunity is well established, the percentage of CLT was lower in zone B than in zone A, and this should exclude a selection bias.

It is therefore quite striking that the typical predominance of CLT in the female gender was virtually voided when comparing the frequency of CLT in females from zone B with males in zone A (26.5% vs 21.5% in the per patient modality of expressing data; 21.6% vs 20.4% in the per nodule modality).

Relationship of CLT with the THY class

This aspect is summarized in Tables 3 and 4. In Table 4, classes were dichotomized (THY2+THY3=benign and THY4+THY5=malignant) in order to increase the size of subgroups. In these tables, data are necessarily reported in the per nodule modality, because in the same patient different nodules may have different cytological diagnoses (i.e. different THY classes). As given in Table 3 that, in typical series of FNAC, around 70% of diagnoses were benign (THY2), around 5% were suspiciously (THY4) or frankly (THY5) malignant, and ~25% indeterminate (THY3); this distribution was similar in the two zones. Because of this relative rarity of the THY4 and THY5 diagnoses, even in the dichotomized format, the number of THY4+THY5 classes remained lower than ten in males of either zone (Table 4).

We evaluated features of CLT in all cases, and it was consistently greater in zone A compared with zone B – but no more than twofold – in each THY class, though statistical significance was reached only in THY2 and THY3 ($P=0.02$ and $P=0.0007$ respectively). Overlapping results were observed analyzing females and males separately. In suspicious or malignant lesions (THY4 and THY5), CLT was slightly higher in zone A; in females the difference was more evident, but not statistically

Table 3 Distribution of the cytological categories (THY2 through THY5) in the thyroid nodules from the two zones.

	Females		Males		All	
	Zone A	Zone B	Zone A	Zone B	Zone A	Zone B
THY2	280 (73.3%)	461 (71.7%)	79 (73.1%)	118 (62.1%)	359 (73.3%)	579 (69.5%)
THY3	88 (23.0%)	153 (23.8%)	22 (20.4%)	64 (33.7%)	110 (22.4%)	217 (26.0%)
THY4	13 (3.4%)	18 (2.8%)	5 (4.6%)	5 (2.6%)	18 (3.7%)	23 (2.8%)
THY5	1 (0.3%)	11 (1.7%)	2 (1.9%)	3 (1.6%)	3 (0.6%)	14 (1.7%)
		B vs A (Df=3; $\chi^2=4.73$, <i>P=0.19</i>)		B vs A (Df=3; $\chi^2=6.35$, <i>P=0.10</i>)		B vs A (Df=3; $\chi^2=5.80$, <i>P=0.12</i>)
TH2+THY3	368 (96.3%)	614 (95.5%)	101 (93.5%)	182 (95.8%)	469 (95.7%)	796 (95.6%)
THY4+THY5	14 (3.7%)	29 (4.5%)	7 (6.5%)	8 (4.2%)	21 (4.3%)	37 (4.4%)
		B vs A (Df=1; $\chi^2=0.43$, <i>P=0.51</i>)		B vs A (Df=1; $\chi^2=0.74$, <i>P=0.39</i>)		B vs A (Df=1; $\chi^2=0.02$, <i>P=0.89</i>)

P values typed boldface italics are borderline significant (between 0.10 and 0.05).

Clinical Study	S Arena and others	Chronic lymphocytic thyroiditis and pollution	172:4	387
----------------	--------------------	---	-------	-----

Table 4 Distribution of chronic lymphocytic thyroiditis in the cytological categories (THY2 through THY5) in the thyroid nodules from the two zones.

	Females		Males		All	
	Zone A	Zone B	Zone A	Zone B	Zone A	Zone B
THY2	76/280 (27.1%) $\chi^2=3.62$, <i>P=0.057</i>	97/461 (21.0%)	15/79 (19.0%) $\chi^2=3.86$, <i>P=0.05</i>	11/118 (9.3%)	91/359 (25.3%) $\chi^2=5.72$, <i>P=0.02</i>	108/579 (18.6%) $\chi^2=11.47$, <i>P=0.0007</i>
THY3	31/88 (35.2%) $\chi^2=6.55$, <i>P=0.01</i>	31/153 (20.3%)	6/22 (27.3%) $\chi^2=4.37$, <i>P=0.04</i>	6/64 (9.4%)	37/110 (33.6%) $\chi^2=0.40$, <i>P=0.53</i>	37/217 (17.1%) $\chi^2=14.36$, <i>P=0.0002</i>
THY4	8/13 (61.5%) $\chi^2=1.55$, <i>P=0.21</i>	7/18 (38.9%)	0/5 <i>P=0.50</i>	1/5 (20.0%)	8/18 (44.4%) $\chi^2=1.31$, <i>P=0.25</i>	8/23 (34.8%) $\chi^2=15.45$, <i>P=0.0001</i>
THY5	1/1 (100%) <i>P=0.42</i>	4/11 (36.4%)	1/2 (50.0%) <i>P=0.40</i>	0/3	2/3 (66.7%) <i>P=0.51</i>	4/14 (28.6%)
THY2+THY3	107/368 (29.1%) $\chi^2=8.56$, <i>P=0.003</i>	128/614 (20.8%)	21/101 (20.8%) $\chi^2=7.33$, <i>P=0.007</i>	17/182 (9.3%)	128/469 (27.3%) $\chi^2=14.36$, <i>P=0.0002</i>	145/796 (18.2%)
THY4+THY5	9/14 (64.3%) $\chi^2=2.64$, <i>P=0.10</i>	11/29 (37.9%)	1/7 (14.3%) $\chi^2=0.01$, <i>P=0.92</i>	1/8 (12.5%)	10/21 (47.6%) $\chi^2=1.31$, <i>P=0.25</i>	12/37 (32.4%)
Total	116/382 (30.4%) $\chi^2=9.82$, <i>P=0.002</i>	139/643 (21.6%)	22/108 (20.4%) $\chi^2=7.04$, <i>P=0.008</i>	18/190 (9.5%)	138/490 (28.2%) $\chi^2=15.45$, <i>P=0.0001</i>	157/833 (18.8%)

P values typed boldface italics are borderline significant (between 0.10 and 0.05). In the B vs A comparison, when only the *P* value is given, this indicates difference analyzed by the Fisher's exact test.

significant (64.3% vs 37.9%, *P*=0.10). Moreover, in each of the two zones CLT was diagnosed in higher number (near doubled in both zones) in suspicious or malignant lesions (THY4+THY5) vs THY2 (*P*=0.02 in zone A and *P*=0.04 in zone B).

Zone A shows a progressive increase in the rate of CLT as the risk of malignancy in the class increases (THY2=25.3% and THY5=66.7%). The increase in zone B starts from the THY3 class and is less evident. The propensity of CLT to be associated with more advanced class of malignancy risk is particularly striking in the females from area A, in whom CLT occurred in two-thirds of the THY4+THY5 class, whereas in the same females CLT occurred in just above one-third of the nodules of the THY2+THY3 class (Table 4).

Multivariate logistic regression analysis

Using a multivariate logistic regression model, after adjusting for gender and THY class, the probability of having CLT significantly increased in nodules from zone A with respect to zone B (OR: 1.704; 95% CI: 1.306–2.222; *P*<0.0001). As expected, female gender was associated with a significantly higher probability of having CLT with respect to male gender after adjusting for residence area and THY class (OR: 2.177; 95% CI: 1.511–3.138; *P*<0.0001). Moreover, after adjusting for gender and residence area, the probability of having CLT significantly increased in THY4+THY5 nodules with respect to THY2+THY3 (OR: 2.358; 95% CI: 1.350–4.116; *P*<0.005).

Discussion

In this study, we have shown that CLT is cytologically demonstrable with statistically significant frequencies in patients from South-Eastern Sicily that stably reside in environmentally different areas, based on the presence or absence in the territory of a large petrochemical complex. In the polluted area, the CLT prevalence is almost twofold greater and with relatively more males being affected. In addition, we have shown a link of CLT with the cytological nature (suspiciously or overtly malignant) of the nodules within the same thyroid, a phenomenon that for its progressiveness was well evident in the polluted area. Indeed, as the nature of the nodule progressed from benign to malignant, through the intermediate class of the indeterminate nature, the rate of associated CLT in nodules from the patients resident in the polluted area progressed from 25% (THY2, benign) to 34% (THY3, indeterminate), 44% (THY4, suspiciously malignant), and 67% (THY5, malignant). Though this progressivity lacks in zone B, nevertheless in zone B patients of classes THY4+THY5 pooled the rate of CLT is double than in the same patients of classes THY2+THY3 pooled (32% vs 18%).

Two Brazilian groups (12, 13) have addressed the association of HT with the petrochemical complex-related pollution by targeting the same area surrounding the petrochemical complex of Capuava (municipality of Santo André, State of Sao Paulo), but two different control areas, though both control areas were located at similar distance (about 16 km away from the complex). Results differed

Clinical Study	S Arena and others	Chronic lymphocytic thyroiditis and pollution	172:4	388
----------------	--------------------	---	-------	-----

because the rate of the endocrine diagnosis of HT was similar to that of the control area (15.6% vs 19.5%) in one study (12) and it was twofold greater (9.3% vs 3.9%) in the other study (13). Even more striking are the inter-study differences in the HT rates for both the identical area surrounding the petrochemical complex (9.3% vs 15.6%) and the nonidentical control area located at similar distance from the study area (3.9% vs 19.5%). Though there were methodological differences in the way the study population had been collected, the contrast is remarkable considering that the criterion for the diagnosis of HT was the same (ultrasonographic changes in thyroid echogenicity plus above-normal serum levels of anti-thyroid peroxidase autoantibodies (TPOAb), with the cut-off level for TPOAb overlapping). The contrasting results between the above studies (12, 13) reinforced our methodological approach of having a direct evidence of the lymphocytic infiltration of the thyroid by targeting patients referred for FNAC. The said twofold difference between areas in one (13) of the two Brazilian studies is in line with the twofold difference in CTL rates between zone A and zone B in our study.

The present work from the south-easternmost province of Sicily (Siracusa) has also to be contrasted with a previous FNAC-based study from the north-easternmost province of Sicily (Messina) (5), though the aim of the latter investigation (5) was unrelated to comparing areas of different pollution exposure. That work (5) spanned the years 1988 through 2007, and was based on 8397 cytologically adequate single or dominant thyroid nodules that were interrogated by US-FNAC always performed by the same operator and cytological reading was always performed by another coauthor. The rate of CLT progressively increased from 1.2% in 1988–1992 to 7.1% in 2003–2007 (5). In a subsequent work (14), we found that in the years 2008–2010, the rate of CLT was 7.3%. At this time, the last available figures are for the year 2011, with a CLT rate of 10.9% (M Rizzo, personal communication). Thus, even in zone B (city of Siracusa), the cytological rate of CLT is at least twice as greater than that in the province of Messina. This would suggest that the city of Siracusa may not be entirely spared by some pollution coming from the petrochemical complex located 15 km north (zone A), the Climiti Hills providing not enough protection.

As discussed elsewhere (5), an increase in the cytological prevalence of CLT has been reported in other countries, such as Greece and Poland with the latest available rate of 13.9% (Greece, in years 1994 compared with 5.9% in years 1985–1986) and 9.7% (Poland, in the

year 2005 compared with 2.6% in 1994). It may not be coincidental that very low cytological rates of CLT are reported in Africa (1.1%, Sudan; 1.6%, Ethiopia; and 2.4%, Kenya), whereas high rates are reported in the oil-rich Middle East (Kuwait, 11.7% in 1986 but 17.8% in 1992; Saudi Arabia, 16.2%) (5).

Strengths of our study include: i) patients resided stably in their corresponding zone; and ii) we provide additional data in the context of the debated issue of CLT being a risk factor for the coexistence of differentiated thyroid cancer, particularly papillary thyroid cancer (15, 16).

Weaknesses of the study are: i) the lack of an histological verification of the nodules, though the malignant nature of the THY4 and THY5 nodules is known to ~75 and 100% respectively; ii) the lack of correlation of CLT with specific environmental pollutants, which were beyond budget for this unfunded investigation; and iii) the lack of biochemical data, particularly serum levels of thyroid-stimulating hormone (TSH). Indeed, some researchers have detected a positive correlation between increasing serum levels of TSH (even within the normal range) and the risk of differentiated thyroid cancer in patients with HT (16, 17).

In summary, our data provide some evidence in favor of the pollution associated with the presence of a petrochemical complex being an important exogenous (or environmental) factor contributing to the development of CLT and, perhaps, also to the association of CLT with thyroid neoplasms.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

The authors thank Dr Gaetano Valastro (Director) and Dr Cirino Mangiameli (Biologist) of A.R.P.A. of Siracusa for their contribution.

References

- 1 Kumar N, Ray C & Jain S. Aspiration cytology of Hashimoto's thyroiditis in an endemic area. *Cytopathology* 2002 **13** 31–39. (doi:10.1046/j.1365-2303.2002.00366.x)

Clinical Study	S Arena and others	Chronic lymphocytic thyroiditis and pollution	172:4	389
----------------	--------------------	---	-------	-----

- 2 Guarneri F & Benvenega S. Environmental factors and genetic background that interact to cause autoimmune thyroid disease. *Current Opinion in Endocrinology, Diabetes, and Obesity* 2007 **14** 398–409. (doi:10.1097/MED.0b013e3282ef1c48)
- 3 Duntas LH. Environmental factors and autoimmune thyroiditis. *Nature Clinical Practice. Endocrinology & Metabolism* 2008 **8** 454–460. (doi:10.1038/ncpendmet0896)
- 4 Benvenega S & Trimarchi F. Changed presentation of Hashimoto's thyroiditis in North-Eastern Sicily and Calabria (Southern Italy) based on a 31-year experience. *Thyroid* 2008 **4** 429–441. (doi:10.1089/thy.2007.0234)
- 5 Rizzo M, Rossi RT, Bonaffini O, Scisca C, Altavilla G, Calbo L, Rosanò A, Sindoni A, Trimarchi F & Benvenega S. Increased annual frequency of Hashimoto's thyroiditis between years 1988 and 2007 at a cytological unit of Sicily. *Annales d'Endocrinologie* 2010 **6** 525–534. (doi:10.1016/j.ando.2010.06.006)
- 6 Latina A, Gullo D, Trimarchi F & Benvenega S. Hashimoto's thyroiditis: similar and dissimilar characteristics in neighboring areas. Implications for the epidemiology of thyroid cancer. *PLoS ONE* 2013 **8** e55450. (doi:10.1371/journal.pone.0055450)
- 7 Bhatia A, Rajwanshi A, Dash RJ, Mittal BR & Saxena AK. Lymphocytic thyroiditis – is cytological grading significant? A correlation of grades with clinical, biochemical, ultrasonographic and radionuclide parameters *CytoJournal* 2007 **4** 1–6. (doi:10.1186/1742-6413-4-10)
- 8 Baloch ZW, LiVolsi VA, Asa SL, Rosai J, Merino MJ, Randolph G, Vielh P, DeMay RM, Sidawy MK & Frable WJ. Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the National Cancer Institute thyroid fine-needle aspiration state of the Science Conference. *Diagnostic Cytopathology* 2008 **36** 425–437. (doi:10.1002/dc.20830)
- 9 Watkinson JC & British Thyroid Association. The British Thyroid Association guidelines for the management of thyroid cancer in adults. *Nuclear Medicine Communications* 2004 **25** 897–900. (doi:10.1097/00006231-200409000-00006)
- 10 Gharib H, Papini E, Paschke R, Duick DS, Valcavi R, Hegedüs L, Vitti P & AACE/AME/ETA Task Force on Thyroid Nodules. American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi, and European Thyroid Association Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules: executive summary of recommendations. *Endocrine Practice* 2010 **16** 468–475. (doi:10.4158/EP.16.3.468)
- 11 Augusto S, Máguas C & Branquinho C. Guidelines for biomonitoring persistent organic pollutants (POPs), using lichens and aquatic mosses – a review. *Environmental Pollution* 2013 **180** 330–338. (doi:10.1016/j.envpol.2013.05.019)
- 12 Camargo RY, Tomimori EK, Neves SC, Knobel M & Medeiros-Neto G. Prevalence of chronic autoimmune thyroiditis in the urban area neighboring a petrochemical complex and a control area in Sao Paulo, Brazil. *Clinics* 2006 **61** 307–312. (doi:10.1590/S1807-59322006000400006)
- 13 de Freitas CU, Grimaldi Campos RA, Rodrigues Silva MA, Panachão MR, de Moraes JC, Waissmann W, Roberto Chacra A, Maeda MY, Minazzi Rodrigues RS, Gonçalves Belchor J *et al.* Can living in the surroundings of a petrochemical complex be a risk factor for autoimmune thyroid disease? *Environmental Research* 2010 **110** 112–117. (doi:10.1016/j.envres.2009.10.009)
- 14 Rizzo M, Sindoni A, Talamo Rossi R, Bonaffini O, Scisca C, Altavilla G, Denaro L, Rosanò A, Saraceno G, Trimarchi F *et al.* Annual increase in the frequency of papillary thyroid carcinoma as diagnosed by fine-needle aspiration at a cytology unit in Sicily. *Hormones* 2013 **12** 46–57.
- 15 Feldt-Rasmussen U & Rasmussen AK. Autoimmunity in differentiated thyroid cancer: significance and related clinical problems. *Hormones* 2010 **9** 109–117. (doi:10.14310/horm.2002.1261)
- 16 Fiore E & Vitti P. Serum TSH and risk of papillary thyroid cancer in nodular thyroid disease. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 1134–1145. (doi:10.1210/jc.2011-2735)
- 17 Boelaert K, Horacek J, Holder RL, Watkinson JC, Sheppard MC & Franklyn JA. Serum thyrotropin concentration as a novel predictor of malignancy in thyroid nodules investigated by fine-needle aspiration. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 4295–4301. (doi:10.1210/jc.2006-0527)

Received 10 October 2014

Revised version received 8 January 2015

Accepted 19 January 2015