Global Pediatric Health
Volume 4: 1–11

DOI: 10.1177/2333794X17736700
journals.sagepub.com/home/gph
SAGE

Risk Factors for Thyroid Cancer in Systemic Lupus Erythematosus

Yutaka Kawano, MD, PhD[1], Meika Nambu, MD[1], Youji Uejima, MD[1], Satoshi Sato, MD, PhD[1], Eisuke Suganuma, MD, PhD[1], Tadamasa Takano, MD, PhD[1], and Tsutomu Oh-ishi, MD, PhD[1]

Abstract

We studied 3 patients with systemic lupus erythematosus (SLE) who developed thyroid cancer (TC). Potential risk factors for TC development was explored. Fifty-three patients with a clinical diagnosis of rheumatic diseases including SLE at our hospital between July 2014 and December 2014 were enrolled. Demographic, clinical, and laboratory findings were retrospectively compared between TC-positive and TC-negative patients. Among rheumatic diseases, lymphadenopathy/splenomegaly at treatment commencement, and lymphadenopathy/splenomegaly, painless ulcer (oral, nasal, or mucosal), and weight loss during the entire study period were precipitating factors. Lower current values of hemoglobin and methylprednisolone pulse therapy favored TC development. In 29 SLE patients, lymphadenopathy/splenomegaly at treatment commencement, lymphadenopathy/splenomegaly and weight loss during the entire study period, urinary granular casts at treatment commencement, and a lower current value of hemoglobin predisposed patients to TC. Several risk factors of TC are present in pediatric SLE. Patients with SLE should be investigated vigorously for TC with ultrasound.

Keywords

allergy/immunology, rheumatology, pulmonology, general pediatrics, infectious diseases

Received September 14, 2017. Accepted for publication September 14, 2017.

Introduction

A high risk of thyroid cancer (TC) in adult-onset systemic lupus erythematosus (SLE) has been reported,[1,2] though a multiple-site international SLE cohort study has provided different conclusions.[3] TC incidence in SLE patients in Scandinavian countries has been reported to be 0.4 to 3.4 per 10^5 subjects.[4] We wished to ascertain the factors promoting TC in childhood-onset SLE. To achieve this goal, symptoms, laboratory findings, medication, and complications were compared between TC-positive and TC-negative patients.

Methods

Ethical Approval of the Study Protocol

The study protocol was approved by the Ethics Committee of Saitama Children's Medical Center (Saitama, Japan; Approval Number 16).

Participants

Fifty-three patients with a clinical diagnosis of SLE, mixed connective-tissue disease (MCTD), juvenile dermatomyositis/polymyositis (DM/PM), Sjögren's syndrome, and antisynthetase syndrome at our hospital between July and December 2014 were enrolled. Participant profiles are shown in Table 1. Diagnoses of SLE, MCTD, DM/PM, Sjögren's syndrome, and antisynthetase syndrome are described elsewhere.[5-9] Remarkably, despite careful examination, TC was observed only in patients with SLE and not in patients with other collagen-based diseases.

[1]Saitama Children's Medical Center, Saitama, Japan

Corresponding Author:
Yutaka Kawano, Department of Infectious Diseases, Immunology, and Allergy, Saitama Children's Medical Center, 1-2 Shintoshin, Chuou-ku, Saitama 330-8777, Japan.
Email: kawano.yutaka@scmc.pref.saitama.jp

Table 1. Patients' Profile.

Disease	Patients (Male–Female)	Age of Onset, Range (Median)	Current Age, Range (Median)
SLE	29 (4:25)	1-14 (12)	13-30 (19)
MCTD	7 (0:7)	2-12 (8)	11-36 (16)
DM/PM	11 (2:9)	3-14 (6)	6-26 (16)
Sjögren's syndrome	4 (2:2)	4-12 (10)	14-22 (16)
Antisynthetase syndrome	2 (1:1)	3-5 (4)	10-20 (15)
Total	53 (9:44)	1-14 (11)	6-36 (17)

Abbreviations: SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease; DM/PM, dermatomyositis/polymyositis.

Examination Items

Medical records of 53 patients were investigated retrospectively. These items were derived from the diagnostic criteria[9] and severity score[10] of SLE.

Symptoms at the Start of Treatment and During the Entire Study Period. The cutaneous and mucosal symptoms that we examined were "butterfly rash," discoid lupus-like plaques, photosensitivity, painless ulcers (oral, nasal, or mucosal), hair loss, Reynaud's phenomenon, peptic ulcers, as well as other cutaneous and mucosal conditions.

Neurological Symptoms. The neurological symptoms that we examined were convulsions, psychological symptoms, organic brain syndrome, cranial-nerve symptoms, mononeuritis multiplex, disturbance of consciousness, cerebrovascular disorders, spinal disorders, aseptic meningitis, as well as other neurological symptoms.

Musculoskeletal Symptoms. The musculoskeletal symptoms that we examined were nondestructive arthritis (more than one), muscle pain, and muscle weakness.

Cardiopulmonary Symptoms. The cardiopulmonary symptoms that we examined were pleurisy, epicarditis, interstitial pneumonia, pulmonary hypertension, pulmonary infarction, pulmonary hemorrhage, as well as other cardiopulmonary symptoms.

Renal Symptoms. The renal symptoms that we examined were rapidly progressive nephritis, renal failure (acute and chronic), nephrotic syndrome, abnormal renal biopsy, as well as other renal symptoms.

Systemic Symptoms. The systemic symptoms that we examined were fever, weight loss, lymphadenopathy, splenomegaly, easy fatigability/general malaise/weakness, and loss of appetite/nausea/vomiting.

Laboratory Data at Treatment Start and Currently

An array of laboratory data were examined: white blood cells, lymphocytes, hemoglobin, platelets, creatinine, CH50, C3, C4, C-reactive protein (CRP), serum amyloid A (SAA), erythrocyte sedimentation rate (ESR), anti-nuclear antibody (ANA; homogeneous, speckled, nucleolar, peripheral, centromere, granular, and nuclear-membrane types), anti-DNA antibody, anti-double-stranded DNA (dsDNA) IgG, anti-Smith (Sm) antibody, anti-U1 ribonucleoprotein (U1RNP) antibody, anti-Sjögren's-syndrome-related antigen A (SSA) antibody, anti-Sjögren's-syndrome-related antigen B (SSB) antibody, anti-cardiolipin antibody, lupus anti-coagulant, biological false-positive (BFP), hemolytic anemia, proteinuria, hematuria, urinary granular casts, thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), thyroglobulin, anti-thyroglobulin antibody, anti-thyroid peroxidase (TPO) antibody, and thyroid-stimulating hormone receptor (TSHR) antibody.

Therapy

Prednisolone was excluded from the present study because all patients received this agent. The drugs that we evaluated were mycophenolate mofetil (MMF), methyl prednisolone (mPSL) pulse therapy, azathioprine (AZA), cyclosporine A (CyA), cyclophosphamide (CYP) pulse therapy, mizoribine, methotrexate (MTX), intravenous immunoglobulin (IVIG), tacrolimus, etanercept, and adalimumab.

Current Therapy and Its Effect

We examined the effects of PSL, nonsteroidal anti-inflammatory drugs, immunosuppressive agents, mPSL pulse therapy, and CYP therapy, as well as other drugs.

Complications

The complications that we looked for specifically were infection, peptic ulcers, diabetes mellitus, hypertension,

compression fractures, osteonecrosis, cerebral infarction, myocardial infarction, disseminated intravascular coagulation, as well as other types of complications.

Statistical Analyses

In the whole analysis, the item "other" (eg, other skin conditions) was excluded from final data unless more than one patient exhibited the same attribute. Patient findings contributing to TC development were compared using the χ^2 test and Fisher's exact test or nonparametric Mann-Whitney test. *P* values were 2-sided, and a significance of .05 was used. Statistical analyses were undertaken with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria).[11]

Methodological Quality

For methodological quality assessment, the checklist set by the Strengthening the Reporting of Observational Studies in Epidemiology[12] and MOOSE guidelines[13] were used.

Results

Case 1

A 24-year-old woman was diagnosed with SLE at the age of 14 years based on fever, butterfly rash, joint pain, swelling of lymph nodes in the neck, reduced numbers of blood cells, anti-nuclear antibody, anti-ds-DNA IgG antibody, anti-DNA antibody, and complement depletion. Renal biopsy was classified as IIIa.

She was treated with PSL, mPSL pulse therapy, AZA, and MMF. When she was 22 years old, she noticed swelling of the thyroid gland. She was diagnosed with papillary TC on ultrasonography. Tumor dimensions were 27 × 19 × 15 mm. After resection of the right lobe of the thyroid gland and dissection of paratracheal lymph nodes, TC did not relapse.

Case 2

Case 2 was a 22-year-old woman. At the age of 12 years, swelling of cervical lymph nodes, fever, erythema, hematuria, anti-ds-DNA IgG antibody, and hypocomplementemia led to the diagnosis of SLE. Renal biopsy was classified as IIIa.

She underwent treatment with PSL, mPSL pulse therapy, and MMF. She was rehospitalized because of relapse of enteropathy at the age of 20 years, and evaluation of the thyroid gland by ultrasound revealed TC. She was diagnosed with papillary TC and tumor dimensions were 9.8 × 9.5 × 15.7 mm. Resection of the right lobe of the thyroid gland, as well as dissection of paratracheal and peribronchial lymph nodes, was successful. Enteropathy was controlled by a combination of mPSL pulse therapy and AZA.

Table 2. Incidence of Thyroid Cancer in Patients With Rheumatic Diseases[a].

	Thyroid Cancer (−)	Thyroid Cancer (+)	Sum
SLE	26	3	29
MCTD	7	0	7
DM/PM	11	0	11
Sjögren's syndrome	4	0	4
Antisynthetase syndrome	2	0	2
Total	50	3	53

Abbreviations: SLE, systemic lupus erythematosus; MCTD, mixed connective tissue disease; DM/PM, dermatomyositis/polymyositis.
[a]*P* = .68.

Case 3

Case 3 was a 14-year-old girl. When aged 14 years, she was diagnosed with SLE based on fever, butterfly rash, joint pain, anti-nuclear antibody, and cytopenia. She received PSL and mPSL pulse therapy. Thereafter, she developed lupus enteritis and was treated further with MMF. She was prescribed with mPSL pulse therapy, cyclosporine, and cyclophosphamide, but noticed a neck tumor 6 months after SLE onset. Ultrasound examination identified a tumor with intra-thyroid calcification. She was diagnosed with papillary TC, and tumor dimensions were 26 × 19 × 39 mm. Concomitant with thyroidectomy, neck lesions equivalent to TC tissue were identified and resected. Postoperatively, she has been treated with PSL without TC relapse.

TC Prevalence Among Patients With Rheumatic Disease

TC was identified exclusively in patients with SLE, but not in those with other rheumatic diseases (Table 2). However, TC prevalence was not increased compared with that for other diseases.

Risk Factors in Patients With Rheumatic Disease

Demographic Features. No items distinguished cancer-positive patients from cancer-free cases.

Symptoms. Lymphadenopathy/splenomegaly at the start of treatment and symptoms present during the entire period, such as lymphadenopathy/splenomegaly, painless ulcers (oral, nasal, mucosal), and weight loss, were precipitating factors for TC development (Table 3).

Laboratory Data. Current hemoglobin levels in cancer patients were significantly lower (P = .0393) than in those who did not have cancer.

Medication. More patients with cancer received mPSL pulse therapy than those who did not have cancer.

Current Therapy and Its Effect. No mediations used in current therapy or their effect had an impact on TC development.

Complications. Prevalence of complications between the 2 groups was not different.

Risk Factors in SLE Patients

Demographic Factors. None of the elements noted in SLE patients favored TC development (Table 4).

Symptoms. Lymphadenopathy/splenomegaly at treatment commencement and lymphadenopathy/splenomegaly and weight loss during the entire period promoted TC development in SLE patients.

Laboratory Data. Urinary granular casts at the start of therapy and currently low hemoglobin levels were contributing factors to TC development.

Medications. Specific examination for SLE revealed no significant differences between patients with or without TC (Table 4).

Current Therapy and Its Effect. We did not find any items that increase the risk of TC with regard to current treatment and its effect.

Complications. Definite comorbidities that differentiate cancer patients from noncancer patients were not identified.

Thyroid Hormone and Autoantibodies

Levels of thyroid hormones (TSH, FT3, FT4) in TC patients were not different from those of cancer-free patients with regard to rheumatic diseases or specifically to SLE (Table 5). Levels of thyroglobulin and autoantibodies (eg, anti-thyroglobulin, anti-TPO, TSHR antibody) in rheumatic disease and SLE were not significantly different (Table 5).

Discussion

Similar to the report that identified AZA as a risk factor for thyroid nodules in SLE,[14] we identified several risk factors that may lead to TC development. Expression of each factor may suggest that TC patients have high SLE activity because these items are associated with severe disease.[10] Furthermore, mPSL pulse therapy is ubiquitous for rheumatic diseases (mainly targeting severe disease) and may contribute to the relatively high distribution among TC patients, with low distribution among cancer-free patients with rheumatic disease. We identified lymphadenopathy/splenomegaly and weight loss to be risk factors, which are systemic conditions (and not organ-specific symptoms) as defined by the severity index.[10] Owing to the small sample size, rheumatic diseases as a whole were associated with more risk factors than SLE alone as a specific single disease entity.

In our investigation, thyroid immunity and thyroid hormones were compared between cancer-positive and cancer-free patients because involvement of the autoimmunity and function of the thyroid gland in cancer development has been suggested by Antonelli et al[1] and Papendieck et al.[15] Our data were not in accordance with their results, and we did not find a distinction in autoantibody levels or hormone levels in the thyroid gland.

With the development of medical technology, identification of thyroid tumors (including benign nodules) has become more common, and some authors recognize benign tumors as "thyroid incidentalomas."[16] However, Papendieck et al suggested a higher prevalence of TC in pediatric thyroid nodules than in adult thyroid nodules.[15] Therefore, we advocate careful investigations to find occult thyroid cancers because failure to detect "true" malignant tumors of the thyroid gland may result in a poor prognosis for SLE patients who carry the potential risk factors to develop them.

Our study had limitations. We evaluated a small number of SLE patients and those with other rheumatic diseases. Using Yates' correction, we analyzed small-sample data in the χ^2 test. Moreover, we used univariate analyses instead of multivariate analyses because an extremely low prevalence of TC did not permit enrolment of sufficient numbers of affected patients (which did not allow for analyses of the confounders that favor TC development). To use logistic regression analyses to study as few as 2 confounders, ≥20 cancer-positive SLE patients

Table 3. Risk Factors for the Development of Thyroid Cancer in Patients With Rheumatic Diseases.

(1) Demographic Features.

	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*
Age	18.0	20.3	.478
Age of onset	10.3	9.3	.692
Family history	7/50	0/3	.952
Sex, male (%)	0.22	0	1

(2) Clinical Symptoms.

	At the Start of Treatment			Entire Period		
	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*
Butterfly rash	29/50	2/3	1	31/50	3/3	.242
Discoid papulosis	2/50	0/3	1	2/50	0/3	1
Photosensitivity	7/50	0/3	1	7/50	0/3	1
Oral, nasal, or mucosal painless ulcer	8/50	2/3	.088	10/50	3/3	.012
Hair loss	3/50	0/3	1	6/50	1/3	.352
Raynaud's phenomenon	7/50	0/3	1	11/50	0/3	1
Peptic ulcer	0/50	0/3	1	10/50	0/3	1
Other skin conditions	5/50	2/3	.043	4/50	2/3	.031
Convulsion	0/50	0/3	1	2/50	0/3	1
Psychological symptom	2/50	0/3	1	2/50	0/3	1
Organic brain syndrome	1/50	0/3	1	0/50	0/3	1
Cranial nerve symptoms	0/50	0/3	1	1/50	0/3	1
Mononeuritis multiplex	0/50	0/3	1	0/50	0/3	1
Disturbance of consciousness	2/50	0/3	1	4/50	0/3	1
Cerebrovascular disorder	0/50	0/3	1	0/50	0/3	1
Spinal disorder	0/50	0/3	1	0/50	0/3	1
Aseptic meningitis	0/50	0/3	1	0/50	0/3	1
Other neurological symptoms	4/50	0/3	1	4/50	0/3	1
Nondestructive arthritis (more than two)	20/50	2/3	.258	19/50	2/3	.555
Muscle pain	3/50	0/3	.567	15/50	0/3	.550
Muscle weakness	15/50	0/3	.549	15/50	0/3	1
Pleurisy	1/50	0/3	1	2/50	0/3	1
Epicarditis	2/50	0/3	1	4/50	0/3	1
Interstitial pneumonia	1/50	0/3	1	2/50	0/3	1
Pulmonary hypertension	2/50	0/3	1	2/50	0/3	1
Pulmonary infarction	0/50	0/3	1	0/50	0/3	1
Pulmonary hemorrhage	0/50	0/3	1	0/50	0/3	1
Other cardiopulmonary symptoms	0/50	0/3	1	0/50	0/3	1
Rapidly progressive nephritis	0/50	0/3	1	0/50	0/3	1
Acute renal failure	0/50	0/3	1	0/50	0/3	1
Chronic renal failure	0/50	0/3	1	0/50	0/3	1
Nephrotic syndrome	0/50	0/3	1	0/50	0/3	1
Renal biopsy abnormal	5/6	2/2	1	8/12	2/3	1
Other renal symptoms	2/50	0/3	1	1/50	0/3	1
Fever	30/50	3/3	.282	30/50	3/3	.282
Weight loss	13/50	1/3	1	13/50	3/3	.024
Lymphadenopathy, splenomegaly	11/50	3/3	.016	11/50	3/3	.016
Easy fatigability, general malaise, weakness	23/50	2/3	.597	24/50	2/3	.611
Loss of appetite, nausea, and vomiting	20/50	2/3	.258	20/50	3/3	.076

(continued)

Table 3. (continued)

(3) Laboratory Data.

	At the Start of Treatment			Current		
	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*
WBC (/μL)	5392	4433	.686	5957	5766	.954
Lymphocytes (/μL)	1456	648	.084	1402	1339	.686
Hb (g/dL)	117	10.4	.143	12.9	10.6	.0393
Plt ($\times 10^4$/μL)	23.3	22.4	1	27.2	30.7	.366
Cre (mg/dL)	0.42	0.55	.0706	0.54	0.48	.289
CH50 (U/mL)	32.6	7.0	.211	36.3	38.8	1
C3 (mg/dL)	64.2	60.0	.186	90.7	86	.677
C4 (mg/dL)	11.4	11.0	.367	19.2	20.3	.531
CRP (mg/dL)	0.975	0.563	.335	0.109	0.423	.341
SAA (μg/mL)	167.5	226.4	.127	10.15	28.67	.114
ESR (mm/h)	47.1	68.0	.193	16.42	23	.901
ANA (fold)	1647	1493	.658	605	40	.524
Homogeneous type	22/43	1/3	1	10/26	1/1	.407
Speckled type	29/44	2/3	1	14/26	1/1	1
Nucleolar type	1/42	0/3	1	0/26	0/1	1
Peripheral type	1/42	0/3	1	0/26	0/1	1
Centromere type	0/42	0/3	1	0/26	0/1	1
Granular type	0/42	0/3	1	1/26	0/1	1
Nuclearmembrane type	0/42	0/3	1	0/26	0/1	1
Anti-DNA Ab (IU/mL)	88.3	135.6	.374	8.35	6.33	.569
Anti-dsDNA IgG (IU/mL)	126.5	183.5	.55	6.84	6.07	.547
Anti-Sm Ab	18/39	2/2	.232	12/24	0/3	.537
Anti-U1RNP Ab	18/36	2/2	1	8/32	0/3	1
Anti-SSA Ab	23/42	1/3	.591	20/37	1/3	.596
Anti-SSB Ab	12/41	1/3	1	11/37	0/3	.548
Anti-cardiolipin Ab	13/35	2/3	.050	3/15	2/2	.132
Lupus anticoagulant	8/34	0/3	1	4/16	0/1	1
BFP	0/5	0/1	1	0/2	0/0	1
Hemolytic anemia	1/45	0/2	1	0/47	0/3	1
Proteinuria (mg/dL)	10.4	22.0	.103	5.20	11.8	.483
Hematuria	5/43	1/3	.056	1/50	0/3	1
Urine granular cast	1/43	2/3	.127	1/50	0/3	1

Abbreviations: WBC, white blood cells; Hb, hemoglobin; Plt, platelet; Cre, creatinine; CH50, 50% hemolytic complement; C3, complement component 3; C4, complement component 4; CRP, C-reactive protein; SAA, serum amyloid A; ESR, erythrocyte sedimentation rate; ANA, anti-nuclear antibody; Ab, antibody; BFP, biological false positive.

(4) Therapy.

	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*
MMF	36/50	3/3	.557
mPSL pulse	17/50	3/3	.049
AZA	17/50	2/3	.290
CyA	9/50	1/3	.920
CYP pulse	4/50	1/3	.261
Mizoribine	14/50	0/3	.557
MTX	11/50	0/3	1
IVIG	4/50	0/3	1
Tacrolimus	2/50	0/3	1
Eterercept	1/50	0/3	1
Adalimab	1/50	0/3	1

Abbreviations: MMF, mycophenolate mofetil; mPSL, methyl prednisolone; AZA, azathioprine; CyA, cyclosporine A; CYP, cyclophosphamide; MTX, methotrexate; IVIG, intravenous immunoglobulin.

(continued)

Table 3. (continued)

(5) Current Therapy and Its Effect.

	Current Therapy			Therapeutic Effect		
	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*
PSL	44/50	3/3	1	44/44	3/3	1
NSAID	10/50	0/3	1	8/10	0/0	1
Immunosuppressants	45/50	2/3	.308	42/42	2/2	1
mPSL pulse	1/50	0/3	1	1/1	0/0	1
CYP pulse	1/50	0/3	1	1/1	0/0	1
Others	11/50	2/3	.145	10/11	1/1	.289
Maximal dose of PSL	9.41	10.17	.327			

Abbreviations: PSL, prednisolone; NSAID, nonsteroidal anti-inflammatory drug; mPSL, methyl prednisolone; CYP, cyclophosphamide.

(6) Complications.

	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*
Infection	9/50	2/3	.105
Peptic ulcer	3/50	0/3	1
Diabetes mellitus	1/50	0/3	1
Hypertension	4/50	0/3	1
Compression fracture	3/50	0/3	1
Osteonecrosis	2/50	1/3	.163
Cerebral infarction	0/50	0/3	1
Myocardial infarction	0/50	0/3	1
DIC	0/50	0/3	1
Others	11/50	1/3	.545

Abbreviations: DIC, disseminated intravascular coagulation.

Table 4. Risk Factors for the Development of Thyroid Cancer in Patients With SLE.

(1) Demographic Features.

	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*
Age	18.9	20.3	.617
Age of onset	10.3	9.3	.692
Family history	3/19	0/2	1
Sex, male (%)	0.154	0	1

(2) Clinical Symptoms.

	At the Start of Treatment			Entire Period		
	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*
Butterfly rash	11/26	1/3	1	16/26	3/3	.532
Discoid papulosis	1/26	0/3	1	1/26	0/3	1
Photosensitivity	5/26	0/3	1	5/26	0/3	1
Oral, nasal, or mucosal painless ulcer	8/26	2/3	.267	9/26	3/3	.062
Hair loss	1/26	0/3	1	4/26	1/3	.446
Raynaud's phenomenon	3/26	0/3	1	4/26	0/3	1
Peptic ulcer	0/26	0/3	1	4/26	0/3	1
Other skin conditions	3/25	2/3	.0733	1/25	2/3	.0232
Convulsion	3/26	0/3	1	3/26	0/3	1

(continued)

Table 4. (continued)

(2) Clinical Symptoms.

	At the Start of Treatment			Entire Period		
	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*
Psychological symptom	3/26	0/3	1	3/26	0/3	1
Organic brain syndrome	1/25	0/3	1	1/25	0/3	1
Cranial nerve symptoms	1/25	0/3	1	0/25	0/3	1
Mononeuritis multiplex	1/25	0/3	1	0/25	0/3	1
Disturbance of consciousness	2/26	0/3	1	2/26	0/3	1
Cerebrovascular disorder	0/26	0/3	1	0/26	0/3	1
Spinal disorder	0/26	0/3	1	0/26	0/3	1
Aseptic meningitis	0/26	0/3	1	0/26	0/3	1
Other neurological symptoms	1/25	0/3	1	2/25	0/3	1
Nondestructive arthritis (more than two)	12/26	2/3	.598	12/26	2/3	.598
Muscle pain	2/26	0/3	1	5/26	0/3	1
Muscle weakness	3/26	0/3	1	3/26	0/3	1
Pleurisy	0/26	0/3	1	1/26	0/3	1
Epicarditis	1/26	0/3	1	3/26	0/3	1
Interstitial pneumonia	0/26	0/3	1	1/26	0/3	1
Pulmonary hypertension	0/26	0/3	1	0/26	0/3	1
Pulmonary infarction	0/26	0/3	1	0/26	0/3	1
Pulmonary hemorrhage	0/26	0/3	1	0/26	0/3	1
Other cardiopulmonary symptoms	0/25	0/3	1	0/25	0/3	1
Rapidly progressive nephritis	0/26	0/3	1	0/26	0/3	1
Acute renal failure	0/26	0/3	1	0/26	0/3	1
Chronic renal failure	0/26	0/3	1	0/26	0/3	1
Nephrotic syndrome	0/26	0/3	1	0/26	0/3	1
Renal biopsy abnormal	5/7	2/2	1	10/11	1/1	1
Other renal symptoms	1/25	1/3	.206	2/26	0/3	1
Fever	18/25	3/3	.551	20/26	3/3	1
Weight loss	6/26	1/3	1	6/26	3/3	.023
Lymphadenopathy, splenomegaly	8/26	3/3	.0452	8/26	3/3	.045
Easy fatigability, general malaise, weakness	12/26	2/3	.598	13/26	2/3	1
Loss of appetite, nausea, and vomiting	12/26	2/3	.598	12/26	3/3	.224

(3) Laboratory Data.

	At the Start of Treatment			Current		
	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*
WBC (/μL)	4276	4433	.496	5413	5766	.474
Lymphocytes (/μL)	1055	648	.371	957	1339	.092
Hb (g/dL)	11.1	10.4	.333	12.8	10.6	.0341
Plt ($\times 10^4$/μL)	16.7	22.4	.35	24	30.7	.112
Cre (mg/dL)	0.47	0.55	.266	1.41	0.48	.282
CH50 (U/mL)	22.1	7.0	.298	32.8	38.8	.618
C3 (mg/dL)	64.2	60.0	.616	84.2	86	.641
C4 (mg/dL)	11.4	11.0	.693	16.1	20.3	.37
CRP (mg/dL)	0.975	0.563	.519	0.098	0.423	.325
SAA (μg/mL)	167.5	226.4	.229	10.05	28.67	.146
ESR (mm/h)	47.1	68.0	.334	16.4	23	.926

(continued)

Table 4. (continued)

(3) Laboratory Data.

	At the Start of Treatment			Current		
	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*
ANA (fold)	1647	1493	.687	769	40	.243
Homogeneous type	15/26	1/3	.573	8/14	1/1	.243
Speckled type	19/26	2/3	1	12/14	1/1	1
Nucleolar type	1/26	0/3	1	0/14	0/1	1
Peripheral type	0/26	0/3	1	0/14	0/1	1
Centromere type	0/26	0/3	1	0/14	0/1	1
Granular type	0/26	0/3	1	1/14	0/1	1
Nuclearmembrane type	0/26	0/3	1	0/14	0/1	1
Anti-DNA Ab (IU/mL)	88.3	135.6	.709	10.23	6.33	.367
Anti-dsDNA IgG (IU/mL)	126.5	183.5	.876	8.73	6.07	.316
Anti-Sm Ab	15/22	2/3	1	6/22	0/3	.554
Anti-U1RNP Ab	6/18	2/3	1	2/20	0/3	1
Anti-SSA Ab	19/24	1/3	.156	17/23	1/3	.215
Anti-SSB Ab	8/23	1/3	1	6/23	0/3	1
Anti-cardiolipin Ab	13/22	2/3	1	3/13	2/2	.095
Lupus anti-coagulant	7/21	0/3	.53	3/12	0/1	1
BFP	0/4	0/1	1	0/0	0/0	1
Hemolytic anemia	1/25	0/3	1	0/26	0/3	.316
Proteinuria (mg/dL)	111	22.0	.139	3.14	11.8	.187
Hematuria	5/25	2/3	.145	1/25	0/3	1
Urine granular cast	1/25	2/3	.023	1/25	0/3	1

Abbreviations: WBC, white blood cells; Hb, hemoglobin; Plt, platelet; Cre, creatinine; CH50, 50% hemolytic complement; C3, complement component 3; C4, complement component 4; CRP, C-reactive protein; SAA, serum amyloid A; ESR, erythrocyte sedimentation rate; ANA, anti-nuclear antibody; Ab, antibody; BFP, biological false positive.

(4) Therapy.

	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*
MMF	21/26	3/3	1
mPSL pulse	9/26	3/3	.060
AZA	12/26	2/3	.598
CyA	1/26	1/3	.200
CYP pulse	2/26	1/3	.298
Mizoribine	10/26	0/3	.532
MTX	2/26	0/3	1
IVIG	2/26	0/3	1
Tacrolimus	2.26	0/3	1
Eterercept	0/26	0/3	1
Adalimab	0/26	0/3	1

Abbreviations: MMF, mycophenolate mofetil; mPSL, methyl prednisolone; AZA, azathioprine; CyA, cyclosporine A; CYP, cyclophosphamide; MTX, methotrexate; IVIG, intravenous immunoglobulin.

(5) Current Therapy and Its Effect.

	Current Therapy			Therapeutic Effect		
	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*
PSL	26/26	3/3	1	26/26	3/3	.237
NSAID	6/24	0/3	1	5/6	0/0	1

(continued)

Table 4. (continued)

(5) Current Therapy and Its Effect.

	Current Therapy			Therapeutic Effect		
	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*
Immunosuppressants	25/26	2/3	.2	25/25	2/2	.2
mPSL pulse	0/25	0/3	1			
CYP pulse	0/25	0/3	1			
Others	0/20	0/2	1	5/6	0/0	1
Maximal dose of PSL	6.63	10.17	.237			

Abbreviations: PSL, prednisolone; NSAID, nonsteroidal anti-inflammatory drug; mPSL, methyl prednisolone; CYP, cyclophosphamide.

(6) Complications.

	Thyroid Cancer (−)	Thyroid Cancer (+)	*P*
Infection	7/25	2/3	.234
Peptic ulcer	0/25	0/3	1
Diabetes mellitus	0/26	0/3	1
Hypertension	3/25	0/3	1
Compression fracture	2/25	0/3	1
Osteonecrosis	2/25	1/3	.293
Cerebral infarction	0/25	0/3	1
Myocardial infarction	0/25	0/3	1
DIC	0/25	0/3	1
Others	4/26	1/3	.446

Abbreviation: DIC, disseminated intravascular coagulation.

Table 5. Thyroid Hormone and Autoantibodies.

(1) Rheumatic Diseases.

	Thyroid cancer (−), Mean ± SD	Thyroid Cancer (+), Mean ± SD	*P*
TSH (μU/mL)	1.38 ± 1.05	1.30 ± 0.26	.908
FT3 (pg/mL)	2.71 ± 0.69	2.50 ± 0.53	.608
FT4 (ng/dL)	1.11 ± 0.17	1.01 ± 0.12	.306
Thyroglobulin (ng/mL)	19.16 ± 12.70	13.53 ± 13.04	.465
Anti-thyroglobulin (IU/mL)	16.05 ± 16.81	12.33 ± 2.08	.707
Anti-TPO (IU/mL)	10.66 ± 8.40	10.66 ± 7.37	.998
TSHR antibody (IU/L)	1.43 ± 7.69	0.50 ± 0.00	.783

Abbreviations: TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TPO, thyroid peroxidase; TSHR, thyroid-stimulating hormone receptor.

(2) Systemic Lupus Erythematosus.

	Thyroid cancer (−), Mean ± SD	Thyroid cancer (+), Mean ± SD	*P*
TSH (μU/mL)	1.38 ± 0.86	1.30 ± 0.26	.869
FT3 (pg/mL)	2.67 ± 0.78	2.50 ± 0.53	.720
FT4 (ng/dL)	1.11 ± 0.17	1.01 ± 0.12	.345
Thyroglobulin (ng/mL)	19.44 ± 13.35	13.53 ± 13.04	.480
Anti-thyroglobulin (IU/mL)	14.82 ± 10.07	12.33 ± 2.08	.679
Anti-TPO (IU/mL)	10.87 ± 9.85	10.66 ± 7.37	.973
TSHR antibody (IU/L)	2.07 ± 6.18	0.50 ± 0.00	.730

Abbreviations: TSH, thyroid-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; TPO, thyroid peroxidase; TSHR, thyroid-stimulating hormone receptor.

are required, which corresponds to ≈200 000 cancer-free SLE patients. Understandably, further expansion of confounders requires large populations.

Conclusion

There are several risk factors for TC development in pediatric SLE. Efforts should be made to find thyroid tumors carefully and intensively and to extract various characteristics among large numbers of TC-positive SLE children to permit multivariate analyses. Our results warrant a wide range of multicenter epidemiological studies instead of the single-center investigation described here.

Authors' Note

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Author Contributions

All authors made a substantial contribution to the work presented in this article. YK and TO contributed to the concept and design, data analysis, and interpretation of data. MM, TU, SS, ES, and TT are instrumental to the data acquisition. All authors edited and approved the article as submitted.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Antonelli A, Mosca M, Fallahi P, et al. Thyroid cancer in systemic lupus erythematosus: a case-control study. *J Clin Endocrinol Metab*. 2010;95:314-318.
2. Zhang M, Li XM, Wang GS, et al. Thyroid cancer in systemic lupus erythematosus: a meta analysis. *Int J Clin Exp Pathol*. 2014;7:6270-6273.
3. Bernatsky S, Ramsey-Goldman R, Labrecque J, et al. Cancer risk in systemic lupus: an updated international multi-centre cohort study. *J Autoimmun*. 2013;42:130-135.
4. Harach HR, Franssila KO, Wasenius VM. Occult papillary carcinoma of the thyroid. A "normal" finding in Finland. A systematic autopsy study. *Cancer*. 1985;56:531-538.
5. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med*. 1975;292:344-347.
6. Fujibayashi T, Sugai S, Miyasaka N, Hayashi Y, Tsubota K. Revised Japanese criteria for Sjogren's syndrome (1999): availability and validity. *Mod Rheumatol*. 2004;14:425-434.
7. Kasukawa R, Tojo T, Miyawaki S, et al. In: Kasukawa R, Sharp GC, eds. Preliminary diagnostic criteria for mixed connective tissue disease. *Mixed Connective Tissue Disease and Antinuclear Antibodies*. Amsterdam-New York, Oxford: Excerpta Medica; 1987:41-47.
8. Marguerie C, Bunn CC, Beynon HL, et al. Polymyositis, pulmonary fibrosis and autoantibodies to aminoacyl-tRNA synthetase enzymes. *Q J Med*. 1990;77:1019-1038.
9. Vasudevan A, Krishnamurthy AN. Changing worldwide epidemiology of systemic lupus erythematosus. *Rheum Dis Clin North Am*. 2010;36:1-13.
10. Hay EM, Bacon PA, Gordon C, et al. The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. *Q J Med*. 1993;86:447-458.
11. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant*. 2013;48:452-458.
12. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. STROBE Initiative. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ*. 2007;335:806-808.
13. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008-2012.
14. Quintanilla-Flores DL, Hernandez-Coria MI, Elizondo-Riojas G, Galarza-Delgado DA, Gonzalez-Gonzalez J, Tamez-Perez HE. Thyroid nodules in Hispanic patients with systemic lupus erythematosus. *Lupus*. 2013;22:1509-1513.
15. Papendieck P, Gruñeiro-Papendieck L, Venara M, et al. Differentiated thyroid cancer in children: prevalence and predictors in a large cohort with thyroid nodules followed prospectively. *J Pediatr*. 2015;167:199-201.
16. Russ G, Leboulleux S, Leenhardt L, Hegedüs L. Thyroid incidentalomas: epidemiology, risk stratification with ultrasound and workup. *Eur Thyroid J*. 2014;3:154-163.