

Thyroid disorders in systemic lupus erythematosus

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SUMMARY Of 319 patients with systemic lupus erythematosus (SLE), nine had thyrotoxicosis, three had hypothyroidism, and two had thyroiditis. This prevalence seems greater than that of similar thyroid disorders seen in the general population. It is suggested that patients with autoimmune thyroid disorders may develop SLE or vice versa. This association requires confirmation by prospective study.

Key words: hyperthyroidism, hypothyroidism, thyroiditis, autoimmune diseases.

Autoimmune disorders often occur together in the same patient. Autoimmune thyroid disorders have been shown to occur in association with connective tissue disorders such as rheumatoid arthritis and Sjögren's syndrome.¹ The association of thyroid disorders with systemic lupus erythematosus (SLE) has not been confirmed. Only isolated cases of this association have been reported.²

It is our impression that there is an increased incidence of thyroid disorders among patients with SLE. This retrospective study is aimed at verifying this impression and identifying the characteristics of SLE in those with disorders of thyroid function.

Materials and methods

All patients who fulfilled the 1982 criteria of the American Rheumatism Association³ for the diagnosis of SLE were included in this review.

Over a 10½ year period of prospective study of SLE from July 1974 to December 1984 we studied 319 patients; 292 were female.

The thyroid disorders reviewed included thyrotoxicosis, hypothyroidism, subacute thyroiditis, and non-toxic goitres. Thyrotoxicosis was diagnosed in patients who presented with a history of marked weight loss, heat intolerance, neck swelling, tremors, eye signs, and other characteristic features of the disease which improved with treatment for thyrotoxicosis.

Many of these patients had such symptoms before

any manifestations of SLE (Table 1), and some had been treated for the thyrotoxicosis elsewhere. (Thyroid function tests in the active phase of thyrotoxicosis were not available in six of the nine patients.)

Hypothyroidism was diagnosed clinically when patients had classical features of lethargy, weight gain, cold intolerance, and bradycardia. Serum thyroxine and thyroid stimulating hormone were measured in all the patients. Subacute thyroiditis was diagnosed when the patients presented with transient, painful enlargement of the thyroid gland in the absence of any known cause for it. One patient had a radioactive iodine uptake scan (Table 1, C2).

Patients were considered to have non-toxic goitres when they had obvious thyromegaly without any clinical or laboratory evidence of altered activity of the thyroid. None of these patients was pregnant or had evidence of iodine deficiency.

Results

Of the 319 patients with SLE, 28 had thyroid disorders (Table 2). Twenty six were females. The temporal relation between the presentation of SLE and thyroid disorder is shown in Table 1.

Eight patients had thyrotoxicosis which was diagnosed from one to 11 years before the onset of SLE. One patient (Table 1, A5) developed thyrotoxicosis five years after the diagnosis of SLE.

All thyrotoxic patients were treated with Neo-Mercazole for one to two years; two subsequently required thyroidectomy. Two eventually became hypothyroid, one after thyroidectomy (Table 1,

Table 1 Characteristics of onset and outcome of illness and antibody levels in patients

Patient No	Age* (years)	Sex	Race	Year of diagnosis		Antithyroid antibody titres†			Outcome of thyroid disorder
				SLE	Thyroid disorder	Year of test	Anti-M (1/400)‡	Anti-TG (1/40)‡	
A. Thyrotoxicosis									
1	37	F	Chinese	1969	1968	1980	<100	2560	Treated NMZ§→hypothyroid On thyroxine
2	42	F	Chinese	1974	1963	—	—	—	Treated NMZ→thyroidectomy →hypothyroid
3	41	F	Chinese	1976	1967	1978	6400	160	On thyroxine Treated NMZ→euthyroid
4	39	M	Chinese	1976	1972	1980	400	640	Relapsed 1977
5	28	M	Chinese	1978	1983	1978	100	320	Treated NMZ→euthyroid
6	36	F	Malay	1982	1971	1980	100	10	Still on NMZ Treated NMZ→thyroidectomy →euthyroid
7	22	F	Chinese	1982	1980	—	—	—	Treated NMZ→euthyroid
8	27	F	Malay	1983	1977	—	—	—	Treated NMZ→euthyroid
9	28	F	Chinese	1984	1979	1984	<100	10	Treated NMZ→euthyroid
B. Hypothyroidism									
1	24	F	Indian	1973	1975	1977	100	80	Remains hypothyroid On thyroxine supplement
2	21	F	Malay	1981	1981	1981	100	2560	On thyroxine supplement
3	25	F	Indian	1983	1983	1983	25 600	1280	On thyroxine supplement
C. Subacute thyroiditis									
1	29	F	Malay	1983	1980	1980	1600	320	Euthyroid presently
2	27	F	Chinese	1983 (mid)	1983 (late)	1983	400	1280	Euthyroid presently

*Age at diagnosis of SLE.

†Anti-M=antimicrosomal antibodies; anti-TG=antithyroglobulin antibodies.

‡Levels above this are considered significant.

§NMZ=Neo-Mercazole.

Table 2 Distribution of thyroid disorders by type and sex of patient

	Male	Female	Total
Thyrotoxicosis	2	7	9
Hypothyroidism	0	3	3
Subacute thyroiditis	0	2	2
Non-toxic goitres	0	14	14
Total	2	26	28

A2). Both these patients later needed thyroxine replacement. One patient (A3) had a relapse of thyrotoxicosis 10 years later. Of the six patients in whom antithyroid antibodies were measured, four had significantly raised titres (Table 1).

Three patients had hypothyroidism. Two were diagnosed when they presented for treatment for SLE, whereas one (Table 1, B1) developed clinical and laboratory evidence of hypothyroidism two years after the diagnosis of SLE. None of the three

patients had a history of preceding thyrotoxicosis. Two patients (Table 1, B2 and B3) had markedly raised titres of antithyroid antibodies.

The two patients with subacute thyroiditis had significantly raised antithyroid antibody titres (Table 1, C1 and C2). Both patients recovered quickly without any treatment with antithyroid drugs and have remained euthyroid. Radioactive iodine scan of patient C2 was negative.

Fourteen patients had non-toxic goitres. All were diffusely enlarged on clinical examination. These patients had goitres before the onset of SLE and have remained euthyroid throughout. There was no change in size or character of the goitres. Antithyroid antibody tests performed in eight of these patients were not raised. These patients are not considered further in this study.

The initial and cumulative manifestations of SLE in the patients with autoimmune thyroid disorders showed a higher incidence of joint and mucocutaneous involvement, lymphadenopathy, and renal manifestations than the rest of the SLE patients.

Table 3 Initial manifestations of SLE in the 14 patients with thyrotoxicosis, hypothyroidism, and subacute thyroiditis*

Manifestations	This study (n=14)	UH group [†] (unpublished data) (n=319)	Singapore group [†] (n=126)	London group [‡] (n=50)
Skin and mucous membrane	93	75.5	52	20
Fever and malaise	93	35.7	48	4
Arthritis or arthralgia	86	45.8	44	62
Renal manifestations	50	18.2	36	—
Lymphadenopathy	21	1.3	8	—
Raynaud's disease	21.4	1.3	—	—
Thrombocytopenic purpura	0	5.3	4	4
Haemolytic anaemia	0	5.3	3	4
Neuropsychiatric	0	5.3	4	4
Gastrointestinal	0	1.3	7	—
Respiratory	0	6.3	7	—
Cardiovascular	0	5.3	7	—

*Figures in table are percentages.

†UH=University Hospital, Kuala Lumpur.

Table 4 Initial laboratory findings in the 14 patients with thyrotoxicosis, hypothyroidism, and subacute thyroiditis

Laboratory test	This study (%)	Singapore group [†] (%)	London group [‡] (%)
Anaemia	30	39	52
Haemolytic anaemia	0	8	12
Leucopenia	0	45	46
Thrombocytopenia	0	26	33
Antinuclear antibodies	86	98	100
Anti-DNA antibodies	100	100	100
	(n=7)		
LE cells	64	83	85
Hypocomplementaemia	71	75	56
Urine red blood cells >5 high power field	43	34	30
24 hour urine protein >1 g/24 h	29	33	26
Raised serum creatinine >150 µmol/l	14	26	10
Serum albumin <30 g/l	21	45	—

Table 5 Cumulative major clinical manifestations of SLE in the 14 patients with functional thyroid disorder

Manifestations	This study (%)	UH group* 1975-1980 [†] (n=67) (%)	London group [‡] (%)
Arthritis	100	53.7	98
Cutaneous	93	71.6	84
Nephritis	59	67.2	40
Pulmonary complications	21	16	52
Pericarditis	7	6.0	20
Neuropsychiatric	7	9.0	50

*UH=University Hospital, Kuala Lumpur.

†Unpublished data.

There were very few initial haematological, cardio-respiratory, or neuropsychiatric manifestations. Some of these patients, however, later developed pulmonary (21%), pericardial (7%), and neuropsychiatric (7%) complications (Tables 3-5).

Discussion

Is thyroid disease associated with SLE? Doniach *et al* in 1965, in a series of 64 cases, found two girls who developed clinical SLE after they had thyroiditis.⁶ Becker *et al* reported a single case of Hashimoto's thyroiditis associated with SLE.² Mulhern *et al* in their retrospective search for associated disorders of Hashimoto's disease found four out of 170 patients who had SLE and five with rheumatoid arthritis and concluded that there was no clear association between SLE and Hashimoto's disease.⁷

Nine of our patients gave a definite history and had signs of thyrotoxicosis which were characteristic of Graves' disease. One patient became thyrotoxic (Table 1, A5) after the onset of SLE. The others had clinical thyrotoxicosis 1-11 years before the confirmation of SLE. Some were still on antithyroid treatment (patient A5), and some had stigmata of previous thyrotoxicosis such as exophthalmos or goitre. Two patients (A1 and A2) became hypothyroid; one (patient A2) a few years after subtotal thyroidectomy.

The prevalence of thyrotoxicosis in our population is not known. In Singapore, where the population structure is similar to ours, the prevalence of thyrotoxicosis is 1% in females and 0.3% in males.⁸ The prevalence of thyrotoxicosis among our SLE patients was 2.7% for females and 5.9% for males. This suggests that among our SLE patients there was

a higher incidence of thyrotoxicosis than in the general population.

Two patients were found to be hypothyroid when they presented for treatment of SLE (patients B2 and B3), while one (patient B1) became hypothyroid two years after the diagnosis of SLE. All required thyroxine supplements. There was no history of previous thyroiditis. In two of the patients the antithyroglobulin and antimicrosomal antibodies were raised. The prevalence of subclinical hypothyroidism in Singapore is 0.4%.⁸ The prevalence of hypothyroidism among our SLE patients was 1.0%. Since thyroid function tests were not carried out routinely in our SLE patients it is possible that there were other patients with subclinical hypothyroidism.

Two patients had transient thyroiditis. Patient C1 had thyroiditis three years before developing SLE. In patient C2 the thyroiditis occurred shortly before the SLE. In both patients the levels of antithyroglobulin and antimicrosomal antibodies were markedly raised. It is too soon to predict if they will develop hypothyroidism eventually (or whether the steroids used in the treatment of SLE will protect them from becoming hypothyroid).

Eleven of the 14 patients were tested for the presence of antithyroid antibodies. Nine of the 11 (81.8%) had raised anti-TG antibodies and five of the 11 (45.5%) had raised anti-M antibodies. Among the local normal population the prevalence is 5.1% for raised antithyroglobulin and 6.4% for raised anti-M.⁹

There were two patients (A6 and A9) who had insignificant antimicrosomal and antithyroglobulin antibody titres. In these patients the thyroid disorder was diagnosed nine and five years before the test. Patient B1 (with low antithyroid antibodies), who had hypothyroidism diagnosed after the onset of SLE, was tested for antibodies two years after the diagnosis and treatment for hypothyroidism. Any antibodies could have become undetectable since it has been reported that thyroid antibody tests frequently become normal several years after patients have been treated.¹⁰

Since SLE is a systemic disorder that can affect any target organ it is interesting to speculate that the thyroid disorders are the result of antithyroid activity of one of the antibodies produced in SLE.¹¹ Patients with SLE may have false positive Wassermann reactions, now considered to be related to the anticardiolipin antibody. Some patients with thyroiditis have a biological false positive Wassermann reaction.¹⁰ It would be interesting if it could be shown that the positive Wassermann reaction in SLE and thyroiditis is due to the same antibody.

These thyroid disorders may be the result of immune injury following deposition of immune

complexes which occurs in the kidney. This could be verified if thyroid biopsies were performed. This type of injury is perhaps unlikely since the vascular arrangement in the thyroid is unlike that of the kidney, which acts as a filter that traps immune complexes or antigens. Many other types of antibodies have been described in SLE but these have not been observed to cause thyroid injury.^{9 11 12}

The antithyroglobulin and antimicrosomal antibodies may have arisen as a result of the SLE autoimmune process. Blake *et al* detected antimicrosomal and antithyroglobulin antibodies in the synovial fluid of 34 of 50 patients suffering from various rheumatological disorders like rheumatoid arthritis, gout, ankylosing spondylitis, and osteoarthritis.¹³ Only four patients had raised levels of the antithyroid antibodies in the serum, suggesting that the antibody was produced in the joints by a pathogenetic mechanism similar to that in the thyroid.¹³ Doniach *et al* found that juvenile autoimmune thyroiditis is associated with antinuclear antibodies in nearly 30% of cases compared with 8% of adults with Hashimoto's disease.⁶ However, only two of the 64 patients with persistent antinuclear antibodies later developed SLE. In most of the autoimmune connective tissue disorders where an association with thyrotoxicosis was considered significant the thyrotoxicosis preceded the autoimmune disorder.¹⁴ The dramatic presentation of thyrotoxicosis could have led to its earlier diagnosis. The immunosuppressive activity of Neo-Mercazole,¹⁵ however, could have delayed or masked the clinical manifestation of SLE.

The patients in this study appear to have more initial malaise, fever, renal disease, and lymph node involvement than the rest of the SLE patients (Table 3). Skin and joint lesions occurred in all these patients, while haematological and neuropsychiatric complications were relatively less frequent. As the number of the SLE patients with thyroid disorders is small firm conclusions cannot be established.

We suggest that there is a positive association between autoimmune thyroid diseases and SLE. The thyroid disorder is similar to that seen in patients without SLE. The underlying pathogenetic mechanism for this association, however, is not clear. Immune complexes have been demonstrated in the kidneys, skin¹⁶ and muscles¹⁷ of patients with SLE. Immune complexes in the thyroid tissue of SLE patients have not yet been described. With the advent of needle biopsies of thyroid nodules¹⁸ the development of this technique for large thyroid glands may help to clarify the association of autoimmune thyroid disorders in SLE.

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