Systemic lupus erythematosus and thyrotoxicosis: a hitherto little recognised association

S RODRIGUÉ, H LABORDE, AND P M CATOGGIO*

From the Rheumatology Section, 6th Chair of Internal Medicine, University Hospital, Buenos Aires Argentina

SUMMARY Six patients are reported in whom systemic lupus erythematosus (SLE) and thyrotoxicosis coexisted. All had four or more American Rheumatism Association criteria (1982) for the diagnosis of SLE and had clinical manifestations and function test results characteristic of hyperthyroidism (except for one who had been thyroidectomised previously). In three patients the diagnosis of hyperthyroidism preceded that of SLE, in two patients both diseases began simultaneously, and only in one was the diagnosis of thyrotoxicosis made after that of SLE. It is suggested that hyperthyroidism associated with SLE may be a form of presentation of thyroiditis. This association may pass unnoticed because of the similarity of some clinical manifestations.

Key words: hyperthyroidism, thyroiditis, Graves' disease, autoimmune diseases.

Coexistence of immune thyroid dysfunction and inflammatory connective tissue disease has been the subject of several reports during the past three decades.¹⁻⁵ Thus Hashimoto's thyroiditis has been described in association with rheumatoid arthritis,⁶ systemic lupus erythematosus (SLE),^{3 7-10} polymyositis-dermatomyositis,¹¹ scleroderma,^{12 13} and Sjögren's syndrome.¹⁴ In addition, antithyroid antibodies are frequently found in different connective tissue diseases^{1 2} as well as in other diseases thought to have an immune basis, even in the absence of clinical manifestations of thyroid disease.¹⁵

Despite the acknowledged autoimmune mechanism in Graves' disease its clinical association with connective tissue disease has not been clearly established. We describe six patients in whom SLE coexisted with clinical and laboratory manifestations of thyrotoxicosis, typical of Graves' disease.

Patients and methods

Five of 93 patients with SLE followed up by our group since 1980, who showed manifestations of thyrotoxicosis, together with a sixth patient with coexistence of both diseases who had been seen in 1973, were included in the study.

All patients were women aged 23 to 41 years and had at least four American Rheumatism Association criteria (1982) for the diagnosis of SLE. In all six patients antinuclear antibodies were looked for by indirect immunofluorescence using rat liver as substrate. Antibodies to native DNA were also sought by passive haemagglutination or complement fixation, or both. Venereal Disease Research Laboratory tests and lupus erythematosus cells were done in all patients.

Five of the six patients had symptoms and signs of hyperthyroidism: diffuse goitre, weight loss, ocular signs, heat intolerance, loss of strength, and other manifestations. A thyroid scan was carried out and ¹³¹I uptake curves constructed. The sixth patient had been thyroidectomised at the time of observation and was euthyroid. When possible, antithyroid antibodies were sought by haemagglutination, and serum concentrations of triiodothyronine and thyroxine by radioimmunoassay.

Results

FEATURES OF SLE

Lupus manifestations were varied and of differing severity (Table 1). Two patients died: one, owing to renal failure related to active glomerulonephritis, and the other, with central nervous system involvement. In two patients the disease had a moderate course without overt renal involvement and with a good response to corticosteroid treatment. The two

Accepted for publication 20 September 1988.

Correspondence to Dr S Rodrigué, Av. Córdoba 2062, 1 Piso 'B', (1120) Buenos Aires, Argentina.

*Deceased.

Table 1 Features of systemic lupus erythematosus

Patient No	Clinical and laboratory findings	Serum findings				1982 ARA criteria score
		ANA*	anti-DNA	VDRL*	LE* cells	
1	Rash, photosensitivity, arthritis, leucopenia, nephritis	+†	—	—	—	6
2	Arthritis, pleuritis, pericarditis, leucopenia	1/300	+	+	+	5
3	Oral ulcers, pleuritis, pericarditis, arthritis, renal and CNS* disease	1/600	+	—	+	7
4	Arthritis, pleuritis, pericarditis, nephritis	1/400	—	—	—	4
5	Oral ulcers, arthritis, pleuritis, pericarditis, nephritis, leucopenia	1/3200	+	+	+	7
6	Rash, photosensitivity, arthritis, nephritis	1/400	+	—	+	6

*ANA=antinuclear antibodies; VDRL=Venereal Disease Research Laboratory test; LE=lupus erythematosus; CNS=central nervous system.

†Titre unknown.

remaining patients, with diffuse proliferative glomerulonephritis, required immunosuppressive treatment. No particular clinical features were common to these patients (Table 1). All had antinuclear antibodies and, in four, anti-DNA antibodies were found.

FEATURES OF THYROTOXICOSIS

In the five patients in whom a thyroid scan was performed diffuse goitre was confirmed and ¹³¹I uptake curves were abnormal (Table 2). Four patients had been adequately controlled with anti-thyroid drugs (methylmercaptoimidazole) and one patient had recently been given β blockers.

ONSET OF INDIVIDUAL DISEASE

In three patients the hyperthyroidism preceded by five years, three years, and six months the onset of lupus manifestations. One of these patients had

undergone thyroidectomy with a diagnosis of Graves' disease before admission to hospital. Even though the results of previous studies were not available, typical unilateral exophthalmus was present during the period of our observation until death (owing to central nervous system involvement related to SLE). In two patients both diseases began simultaneously and their coexistence was not diagnosed earlier owing to overlap of clinical manifestations: fever, weight loss, tachycardia, muscle weakness, and tenderness. In only one patient the diagnosis of thyrotoxicosis was made nine years after that of SLE.

Discussion

The association of diffuse goitre with normal or low thyroid function in SLE is well recognised.^{3,4} The coexistence of SLE and thyrotoxicosis is less familiar, however.¹⁶⁻¹⁹ The clinical association between

Table 2 Features of thyroid disorders

Patient No	Clinical thyrotoxicosis	Exophthalmus	Diffuse goitre	Thyroid scan*	¹³¹ I uptake (%)†			T3‡ (nmol/l)	T4‡ (nmol/l)	Antithyroid antibodies	
					1 h	24 h	48 h			AT‡	AMF‡
1	Yes	Yes	Yes	Yes	37	90	93	ND‡	ND	1/100	1/40
2	Yes	No	Yes	Yes	14	95	90	ND	ND	ND	ND
3	§	Yes	§	§	—	—	—	ND	ND	ND	ND
4	Yes	No	Yes	Yes	35	73	70	ND	ND	ND	ND
5	Yes	No	Yes	Yes	24	66	69	3.6	257	1/100	1/12000
6	Yes	No	Yes	Yes	14	53	51	11.6	257	1/40	1/800

*Large, diffuse distribution.

†Normal value of ¹³¹I uptake is 8% at one hour, <35% at 24 hours, and <32% at 48 hours.

‡T3=triiodothyronine (normal value 1.2-3.4 nmol/l); T4=thyroxine (normal value 51-142 nmol/l); AT=antithyroglobulin; AMF=antimicrosomal fraction; ND=not done.

§Previous total thyroidectomy.

these two disorders has only recently been established. Goh and Wang reported thyroid disorders in 14 out of 319 patients with SLE, nine of whom had clinical evidence of hyperthyroidism consistent with Graves' disease.²⁰ In eight of these patients thyroid disease preceded the manifestations of SLE by one to 11 years. Only two of these patients with thyrotoxicosis then developed hypothyroidism, one after total thyroidectomy. Miller *et al* found thyroid disease in 25 of 332 patients with SLE—a clinical prevalence of 7.5%.²¹ Of these 25, 22 were hypothyroid and three were hyperthyroid. They studied 175 of the remaining 307 clinically euthyroid patients with SLE with a functional thyroid test and found that 44 had either subclinical hypothyroidism or biochemical primary hypothyroidism and that five others had hyperthyroxinaemia. These features suggest that clinical and functional thyroid dysfunction in SLE is more common than expected. The association of thyrotoxicosis with other autoimmune diseases has not been reported frequently. Marshall *et al* reported clinical hyperthyroidism in four out of 42 patients (10%) with idiopathic thrombocytopenic purpura, and in two additional patients they found a biochemical 'latent' Graves' disease.¹⁹ Thomas and Croft described hyperthyroidism in five of 59 patients with giant cell arteritis.²² Thyroid disease preceded the onset of arteritis in three cases and, in two, onset was simultaneous.

The association of SLE with thyrotoxicosis was higher among our patients than that reported by other authors. Either ethnic factors or the difficulty of identifying the coexistence of these two disorders owing to their similar clinical manifestations may account for these different prevalences. We did not study our remaining patients with SLE with thyroid function tests, thus we do not know the overall prevalence of functional thyroid disorder in our patients with SLE.

The association of Hashimoto's thyroiditis with different autoimmune diseases is well known, and even though the former may begin clinically with transient hyperactivity, this thyroiditis usually manifests with hypoactivity. It is now accepted that there is a close relation between Graves' disease and Hashimoto's thyroiditis and that both diseases may be considered as different forms of the same process.^{23 24} The fact that longstanding thyrotoxicosis has been seen in patients with thyroid glands, which on microscopy proved to be Hashimoto's thyroiditis,²³ makes it hard to draw clear cut distinctions between these two thyroid disorders; thus suggesting the term 'Hashi-Graves'. It would not be unreasonable, therefore, to suggest that our patients had SLE and perhaps one form of presentation of Hashimoto's thyroiditis.

On the other hand, drug induced SLE related to the use of the antithyroid drug propylthiouracil has been reported.^{25 26} True coexistence of both diseases might have been erroneously attributed to this observation. None of our patients had been treated with propylthiouracil, and only two patients had been given methylmercaptoimidazole before developing SLE; this drug and propylthiouracil are members of the thionamide class. Association of the former drug with induced SLE has not been clearly established.²⁶ One of the two patients given methylmercaptoimidazole had discontinued antithyroid treatment at least one month before the onset of lupus, and the other patient died owing to renal failure related to active glomerulonephritis.

The early differential diagnosis between SLE and thyrotoxicosis can be difficult because they share some similar clinical manifestations. Perhaps routine inclusion of clinical and functional thyroid tests in patients with SLE and vice versa would reveal a larger number of cases of overlap.

References

- Anderson J R, Goudi R B, Gray K G, Buchanan W W. Antibody to thyroglobulin in patients with collagen diseases. *Scott Med J* 1961; 6: 449-56.
- Hijmans W, Doniach D, Roitt I M, Holborow E J. Serological overlap between lupus erythematosus, rheumatoid arthritis and thyroid autoimmune disease. *Br Med J* 1961; ii: 909-14.
- White R G, Bass B H, Williams E. Lymphadenoid goitre and the syndrome of systemic lupus erythematosus. *Lancet* 1961; i: 368-73.
- Becker K L, Ferguson R H, McConahey W M. The connective tissue diseases and symptoms associated with Hashimoto's thyroiditis. *N Engl J Med* 1963; 268: 277-80.
- Mulhern L M, Masi A T, Shulman L E. Hashimoto's disease: a search for associated disorders in 170 clinically detected cases. *Lancet* 1966; ii: 508-11.
- Thomas D J B, Young A, Gorsuch A N, Bottazzo G F, Cudworth A G. Evidence for an association between rheumatoid arthritis and autoimmune endocrine disease. *Ann Rheum Dis* 1983; 42: 297-300.
- Weetman A P, Walport M J. The association of autoimmune thyroiditis with systemic lupus erythematosus. *Br J Rheumatol* 1987; 26: 359-61.
- Larsen R A, Godal T. Family studies in systemic lupus erythematosus. IX. Thyroid disease and antibodies. *J Chronic Dis* 1972; 25: 225-33.
- Garber J J, Worthington J W, Randall R V, Kierland R R. Lupus erythematosus and Hashimoto's thyroiditis. *Postgrad Med J* 1969; 46: 100-5.
- Francis D A. Pure red-cell aplasia: association with systemic lupus erythematosus and primary autoimmune hypothyroidism. *Br Med J* 1982; 284: 85.
- Guido J, Andrada J, Capdevielle I F, Mattera R, Bozzolasco C. Thyroiditis autoimmune y dermatomiositis. *Medicina (B Aires)* 1964; 24: 340-3.
- Khal L E, Medsger T A Jr, Klein I. Prospective evaluation of thyroid function in patients with systemic sclerosis (scleroderma). *J Rheumatol* 1986; 13: 103-7.
- Gordon M B, Klein I, Dekker A, Rodnan G P, Medsger T A Jr. Thyroid disease in progressive systemic sclerosis: increased

- frequency of glandular fibrosis and hypothyroidism. *Ann Intern Med* 1981; **95**: 431-5.
- 14 Karsh J, Paulidis N, Weintraub B D, Moutsopoulos H M. Thyroid disease in Sjögren's syndrome. *Arthritis Rheum* 1980; **23**: 1326-9.
- 15 Crowe J P, Christensen E, Butler J, *et al*. Primary biliary cirrhosis: the prevalence of hypothyroidism and its relationship to thyroid antibodies and sicca syndrome. *Gastroenterology* 1980; **78**: 1437-41.
- 16 Papadopoulos C, Jiji R, Maher E. Lupus erythematosus and hyperthyroidism. *Am J Dis Child* 1969; **118**: 621-5.
- 17 Cheah J S, Chia B L, Tay H H, Tan B Y. Hyperthyroidism in systemic lupus erythematosus. *Med J Aust* 1970; **2**: 1029-30.
- 18 Oren M E, Cohen M S. Immune thrombocytopenia, red cell aplasia, lupus, and hyperthyroidism. *South Med J* 1978; **71**: 1577-8.
- 19 Marshall J S, Weisberger A S, Levy R P, Breckenridge R T. Coexistent idiopathic thrombocytopenic purpura and hyperthyroidism. *Ann Intern Med* 1967; **67**: 411-4.
- 20 Goh K L, Wang F. Thyroid disorders in systemic lupus erythematosus. *Ann Rheum Dis* 1986; **45**: 579-83.
- 21 Miller F W, Moore G F, Weintraub B D, Steinberg A D. Prevalence of thyroid disease and abnormal thyroid function test results in patients with systemic lupus erythematosus. *Arthritis Rheum* 1987; **30**: 1124-31.
- 22 Thomas R D, Croft D N. Thyrotoxicosis and giant-cell arteritis. *Br Med J* 1974; **iii**: 408-9.
- 23 Fatourehchi V, McConahey W, Woolner L B. Hyperthyroidism associated with histologic Hashimoto's thyroiditis. *Mayo Clin Proc* 1971; **46**: 682-9.
- 24 Tamai H, Nakagawa T, Ohsako N, *et al*. Changes in thyroid functions in patients with euthyroid Graves' disease. *J Clin Endocrinol Metab* 1980; **50**: 108-12.
- 25 Librik L, Sussman L, Bejar R, Clayton G W. Thyrotoxicosis and collagen-like disease in three sisters of American Indian extraction. *J Pediatr* 1970; **76**: 64-8.
- 26 Amrhein J A, Kenny F M, Ross D. Granulocytopenia, lupus-like syndrome, and other complications of propylthiouracil therapy. *J Pediatr* 1970; **76**: 54-63.