Systemic Lupus Erythematosus and Thyroid Disease

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Autoimmune diseases can be divided into organ-specific and systemic illness. The systemic inflammatory autoimmune diseases include rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, polymyositis and systemic sclerosis [1]. One of the commonest organs to be affected by organ-specific autoimmune injury is the thyroid gland. The occurrence of two or more organ-specific autoimmune diseases in a single adult person is known as type 2 autoimmune polyglandular failure [2]. If we exclude patients with overlap syndrome, systemic autoimmune diseases do not commonly occur in the same patient [3]. Whether concomitant organ-specific and systemic autoimmune diseases occur more often by chance than expected is a controversial issue. In particular, a large body of conflicting data has accumulated concerning the relationship between thyroid disease and SLE. We review here the available data regarding the association of SLE and thyroid disease.

Do SLE patients have a higher prevalence of thyroid disease or thyroid antibodies?

SLE and hypothyroidism

Numerous small series [4,6–11] and case reports [12–17] have associated SLE with hypothyroidism – both subclinical (normal thyroxine, high thyroid-stimulating hormone) and clinical (low T4, high TSH). Chan and colleagues [4] studied 69 patients with SLE and found that 13% had subclinical hypothyroidism and 4.3% clinical hypothyroidism. According to the Whickham study [5], the prevalence of subclinical hypothyroidism in females above the age of 18 was 7.5% and clinical hypothyroidism 1%. Pyne and Isenberg [6] reported a higher prevalence of hypothyroidism in 300 patients with SLE (5.7%) than in a normal population (1%). In two studies from Korea [7] and Singapore [8] that investigated SLE, 9.5% of the 63 Korean patients [7] and 3.9% of the 129 from Singapore had Hashimoto's thyroiditis. Tsai et al. [9] also found Hashimoto's thyroiditis in 4 of 45 SLE patients (8.8%) investigated. In another series of 70 patients with SLE, thyropathy was found in 15 patients (21.4%) [10]. Miller and co-workers [11] found that in 332 SLE patients the prevalence of diagnosed hypothyroidism (6.6%) was unexpectedly high, although the overall prevalence of diagnosed thyroid disease (7.5%) was similar to that in other female populations. Pedersen and Kerlin [12] described two girls with SLE who developed clinical hypothyroidism with elevated TSH and decreased thyroid function test. Gonzalez Gay et al. [13] reported an SLE patient with autoimmune thyroiditis. Additional sporadic cases of SLE and hypothyroidism have been described [14–17]. In 42 patients with juvenile SLE, no difference in thyroid hormone level was observed between patients and controls [18]. Table 1 presents the prevalence of clinical hypothyroidism among patients with SLE. In summary, the prevalence of subclinical and clinical hypothyroidism in patients with SLE is higher than in the normal population.

Table 1. Prevalence of hypothyroidism among patients with SLE*

Ref. No.	No. of SLE patients	Percent of patients with clinical hypothyroidism
4	69	4.3%
6	300	5.7%
7	63	9.5%
8	129	3.9%
9	45	8.8%
10	70	21.4%
11	332	6.6%

* The prevalence of hypothyroidism in the normal population is 1% [5].

SLE and hyperthyroidism

Fewer data are available regarding SLE and hyperthyroidism. Boey et al. [8] used thyroid function tests to screen 129 patients with SLE and discovered hyperthyroidism in 8.9%. Goh and Wang [19] found that 9 of 319 patients with SLE had thyrotoxicosis, a prevalence higher than in the general population.

Also reported is the number of cases in which SLE and thyrotoxocosis coexist [20–25]. Rodrigue and associates [20] reported 6 patients, while other authors noted another 10 patients with clinical association of SLE and hyperthyroidism [21–23]. Two cases of Graves' disease in women with SLE were also published

SLE = systemic lupus erythematosus
T4 = thyroxine
TSH = thyroid-stimulating hormone

[24,25]. Thus, although there are some cases of SLE and hyperthyroidism, more information is needed.

SLE and antithyroid autoantibodies

Several recent studies have addressed the question of whether antithyroid antibodies, antithyroid peroxidase (anti-TPO, formally known as antimicrosomal) or antithyroglobulin, are present in SLE patients. Among 69 SLE patients, positive anti-TPO was detected in 23.2% [4]. Population studies have shown the prevalence of TPO antibodies to be around 10% in females [5]. Park et al. [7] evaluated 63 SLE patients and found a prevalence of 27% antimicrosomal and/or antithyroglobulin autoantibodies. In a different series of 129 SLE patients 32.2% had antimicrosomal and antithyroglobulin antibodies [8]. Thyroid antibodies were detected in 21 of 45 SLE patients (46.7%) from China [9]. In a single study that examined children with SLE, 11 of 35 patients (31%) had anti-TPO while 29% had antithyroglobulin [26]. The rate of positivity was much higher than in normal children studied by others. Cases of SLE with antithyroid antibodies have been reported [12,14].

Vianna and colleagues [27] studied 100 patients with SLE during a 6 month period, and found, overall, that patients with SLE (21%) and controls (16%) had a similar prevalence of antithyroid antibodies. However, antithyroglobulin antibodies were found in 11% of patients with SLE and in only 2% of controls. The levels of antimicrosomal antibodies were also different, but this difference did not reach statistical significance [27]. In another study using an adequate control population of 41 SLE patients, 5 had antithyroglobulin, 6 had anti-TPO only and 10 had both [28]. Of the 41 matched controls 1 had antithyroglobulin only, 2 had anti-TPO only and 8 had both [28]. An association was noted between the clinical activity of SLE and antithyroid antibodies [29]. Five of 11 active SLE patients had either antithyroglobulin or anti-TPO, while none of 10 inactive SLE patients had either [29].

In a study of 29 SLE Japanese patients, 7 of 24 patients had anti-TPO, but their sera did not inhibit the activity of thyroid peroxidase [30]. This is in contrast to patients with thyroid disease in whom inhibition was found. A recent study that examined this question found that 14 of 37 patients with SLE had anti-TPO in their sera, but inhibition of the enzymatic activity of thyroid peroxidase by these antibodies from SLE patients was no different from the inhibition by sera from controls without anti-TPO. In contrast, sera from patients with autoimmune thyroid disease inhibited activity well [31].

Antibodies to other thyroid antigens have been only rarely assayed in SLE. Thyroid-stimulating immunoglobulin and thyroid-binding inhibitory immunoglobulin, both of which target the TSH receptor, have been found respectively in the sera of 5 and 10 of 28 SLE patients [32]. A single SLE patient has been reported with antibodies to TSH [33].

In summary, the prevalence of anti-TPO and especially antithyroglobulin antibodies is higher in SLE patients than in controls, although their inhibitory activity is less than in thyroid disease.

anti-TPO = antithyroid peroxidase

Do patients with autoimmune thyroid disease have a higher prevalence of SLE?

Whether or not patients with autoimmune thyroid disease have an excess of SLE has not been extensively studied. A retrospective study investigated the frequency of autoimmune diseases in 218 patients with autoimmune thyroid disease and found that 13.7% had one or more autoimmune disease [34]. The two most frequent autoimmune diseases were lupus and Sjögren's syndrome. Few case reports have associated thyroid disease with SLE. One reports a patient with Graves' disease who developed SLE a year later [35]. Another describes a girl with autoimmune thyroiditis that developed into SLE [36].

There are also reports that the common treatment of hyperthyroidism with thiamazole and propylthiouracil can induce a lupus erythematosus-like syndrome with positive antinuclear and anti-double stranded DNA antibodies [37]. A condition fitting the diagnostic criteria of SLE after treatment with propylthiouracil was also reported [38]. However, there is insufficient information to unequivocally answer whether patients with autoimmune thyroid disease have a higher prevalence of SLE.

Discussion

SLE is a disease of unknown etiology in which tissues and cells are damaged by pathogenic autoantibodies and immune complexes [39]. In areas of iodine sufficiency, autoimmune disease is the most common cause of hypothyroidism [39]. Although thyroid antibodies and thyroid disease are not included in the classification criteria for SLE, it is reasonable to explore whether patients with SLE have a higher prevalence of hypothyroidism and thyroid disease than that in the normal population. Even though the demographic group at risk for SLE, i.e., young to middle-aged women, is the same group that is at risk for thyroid disease, several large-enough series [4,6–11] and case reports [12–17] have shown that the prevalence of hypothyroidism is higher in SLE patients than in the general population of women. Few studies had a control group of the same age and gender with which to compare the patient cohort [27,28].

The mechanism that results in thyroid follicular destruction involves T cell-mediated antibodies that fix complement or inhibit thyroid cell function [39]. Studies on antibodies directed towards the thyroid in patients with SLE indicate an increase in these antibodies, when compared with age, gender and race-matched controls [4,7–9,12,14,26]. Of interest is a study that documented a high incidence of autoimmune thyroid disease in MLR lpr/lpr mice [40]. These mice develop a disease that resembles human SLE. The finding that the mice develop both an SLE-like syndrome and autoimmune thyroid disease demonstrates that these diverse manifestations of autoimmunity can develop from the same immunologic defect.

The issue of an association between SLE and hyperthyroidism [8,19,20–25], and whether patients with autoimmune thyroid disease have a higher prevalence of SLE remains open and requires confirmation by prospective studies.

Conclusion

Patients with SLE have a higher prevalence of hypothyroidism than

that in the normal population. The presence of that condition was associated with a higher frequency of both antimicrosomal and antithyroglobulin antibodies. Physicians caring for SLE patients should remain alert to the possible development of hypothyroidism. This association may pass unnoticed because of the similarity of some clinical manifestations and because the manifestations may be subtle, especially early in the disease. Thyroid function and TPO-antibody tests should be performed as part of the biochemical and immunologic profile in SLE. For those who are at high risk (females, high TSH, positive TPO-antibodies) a thyroid function follow-up is essential and appropriate treatment should be given in due course.

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