The incidence of serologic evidence of antecedent autoimmune thyroiditis in asymptomatic patients referred to an outpatient rheumatology consultation clinic for a positive antinuclear antibody test

A common cause of referral to outpatient rheumatology clinics at our institution is the presence of a low titer positive antibody test (ANA) in the absence of other symptoms and signs of connective tissue disease. In 1961, White *et al*., reported on the presence of "antinuclear factor" in 5 out of the 40 patients with "lymphadenoid goiter" (Hashimoto's thyroiditis) and thus established the relationship between Hashimoto thyroiditis and antinuclear antibodies (1).

The purpose of the present study is to determine what percentage of patients referred to our outpatient rheumatology clinic with a positive ANA have laboratory evidence of prior autoimmune thyroiditis.

The study involved 17 patients from our rheumatology consult clinics at the University of New Mexico Health Sciences Center (UNMHSC). Our study was approved by the Human Research Review Committee of the UNMHSC in March 2002. Informed consent was obtained for all study patients. Seventeen patients were identified from our outpatient rheumatology consult clinic who were referred because of a positive ANA test and were screened for the absence of any connective tissue disease. These patients were subsequently tested for thyroid function by a TSH test and evidence of antecedent autoimmune thyroiditis by the measurement of anti-thyroglobulin and anti-peroxidase antibodies.

Anti-thyroglobulin (anti-thryrog) and anti-peroxidase (anti-tpo) antibody titers were determined using enzyme linked immunosorbent assay. ANA was determined by indirect immunofluorescence using HEp-2 cells as substrate and defined as positive when detected at a serum dilution of more then 1:40 (2, 3).

The average age of the patients in our study was 51 years. The group consisted of 15 females and 2 males. The average ANA titer was 1:155 with a range of 1:40 to 1:640, 8 of 17 (47%) had a titer $\geq$ 1:160.

The most common pattern in our study was homogenous which occurred in 14 out of 17 patients Speckled was the next most common with 3 out of 17 patients showing this pattern either alone or in combinations with a homogenous pattern. Lastly, a centromere pattern was noted in 1 of the 17 patients.

The overlap between endocrine disorders and the autoimmune rheumatic diseases has been well studied. This is particularly true with respect to autoimmune thyroid disease. An increased prevalence of autoimmune thyroiditis has been found in patients with rheumatoid arthritis, systemic lupus erythematosus, scleroderma, Sjögren's syndrome, giant cell arteritis, and possibly even in patients with eosinophillic fascittis (4).

This association is interesting, as it implies in overlap between systemic autoimmune disease (thought to be secondary to a breakdown in peripheral tolerance) and organ specific autoimmune diseases (thought to be secondary to a loss of central tolerance). White *et al*. reported on the presence of "antinuclear factor" in 5 out of the 40 patients with "lymphadenoid goiter" (i.e. Hashimoto's thyroiditis) (1). Thus, the relationship between autoimmune thyroiditis and antinuclear antibodies has long been known. In one study, which involved 168 patients with autoimmune thyroiditis, ANA positivity was found in 58 (35%) of patients. However, many of these same patients were also found to have anti-Ro antibodies, anti-La antibodies, anti-dsDNA antibodies, as well as anticardiolipin antibodies and leukopenia (5). Thus, it is likely that significant portions of these patients in this study had systemic lupus had erythematosus as a cause of positive ANA testing in addition to autoimmune thyroiditis. This overlap can be identified in similar studies as well (6-12).

The purpose of our study was to determine what percentage of asymptomatic patients with a positive ANA test had laboratory evidence of prior autoimmune thyroiditis (i.e. Hashimoto's thyroiditis). The results of our study indicate that patients referred to our clinics for a positive ANA have a high incidence of serologic evidence of antecedent thyroiditis (3). In the study by Tektonidou *et al*., which involved 168 patients with autoimmune thyroiditis, in which 58 (35%) were found to have a positive ANA compared with 9% of healthy controls (5). This is also significantly higher than Inamo's study, which involved 12 children with Hashimoto's thyroiditis. (11) In this study, a positive ANA was found in 4 out of the 12 patients or 33%.

The goal of this study was not to ascertain the overall incidence of a positive ANA test in patients with serologic evidence of antecedent thyroiditis, but rather to determine the incidence of serologic evidence for antecedent thyroiditis in patients referred for a positive ANA test. These patients did not meet any criteria for a collagen vascular disease which one would associate with a positive ANA. Thus, the overall incidence of a positive ANA in the total population with antecedent thyroiditis is probably lower and may be in the range of the studies referred to above.

We conclude that rheumatologists should be alert to the possibility of antecedent autoimmune thyroiditis as an explanation for a positive antinuclear antibody test in asymptomatic patients in a rheumatology clinic. Furthermore, the high incidence of a low titer ANA in this population represents an important link between an organ specific autoimmune disease, autoimmune thyroiditis, and autoimmune disease of a more systemic nature, such as systemic lupus erythematosus.

Table I. Characteristics of study patients.

Age	Sex	Comorbitities	Anti-tpo (< 34 normal)	Anti-thyrog (< 39 normal)	ANA titer	Pattern
45	F	DM, DVT	24	0	1:160	Homogen
63	F	DEP, HTN	222	24	1:40	Homogen
45	M	Gout, HTN	127	0	1:40	Homogen
53	F	DM, HTN	1000	203	1:80	Homogen
26	M	NA	1000	661	1:80	Homogen, speckled
75	F	FIB	65	0	1:160	Homogen
43	F	OSA, GERD	943	0	1:320	Centromere
52	F	SK, HSV	600	27	1:320	Homogen
45	F	HTN	112	0	1:40	Homogen
64	F	HTN	90	0	1:640	Homogen
25	F	HTN	94	0	1:4	Homogen
66	F	OA, HTN	0	0	1:160	Homogen
51	F	HTN, GERD, OA	54	24	1:180	Homogen
51	F	HTN, GERD	41	24	1:40	Speckled
41	F	DEP, OSA	39	19	1:40	Homogen
43	F	GERD, OSA	943	0	1:320	Centromere
79	F	RSD, OA	820	-	1:40	Speckled

HTN: hypertension; DEP: depression; DM: Type 2 diabetes mellitus; OSA: obstructive sleep apnea; RDS: reflex sympathetic dystrophy; GERD: gastroesophageal reflux disease; OA: osteoarthritis; SK: seborrheic keratosis; Fibro: fibroymyalgia; DVT: prior deep venous thrombosis; HSV: herpes simples virus type II; OB: obesity.

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Disseminated candidiasis in systemic lupus erythematosus

Sirs,

A 47-year-old female patient was admitted to the hospital because of anorexia, nausea and fatigue. She had been diagnosed as having systemic lupus erythematosus (SLE) 10 years ago when she was pregnant. She was prescribed prednisolone 5-10mg, hydroxychloroquine 200mg for 2 years recently. Total dose of prednisolone was about 6900mg without any other immunosuppressive treatment.

On admission, laboratory test showed WBC 3400/uL (neutrophil 80%, lymphocyte 17.1%), hemoglobin 8.9 g/*dl*, platelets 96000/uL, ESR 39 mm/hr, total protein 4.61 g/*dl*, albumin 2.33 g/*dl*, AST 162 IU/L, ALT 52 IU/L, ALP 166 IU/L (normal value: n.v. 38-94), serum creatinine and electrolytes were within normal; 24-hours proteinuria was 646.8 mg/day. Immunologic studies showed C3 29.5 mg/*dl* (n.v. 88-155), C4 < 10 mg/*dl* (n.v. 13-35), anti-ds DNA 181 IU/mL (n.v. < 7.0), C-reactive protein 82.3 mg/*dl* (n.v. 0-5), anti-nuclear antibody 1:640. There was no evidence of viral hepatitis. On abdominal sonogram, there was hepatomegaly with diffuse increased echogenesity, without any lesions. Initial diagnosis was SLE with increased disease activity. Treatment with prednisolone (1mg/kg/day) was initiated from 2nd hospital day.

On the 14th hospital day, sudden high fever (39.7 ºC), dyspnea, oliguria, tachycardia, hypotension (70/50 mmHg) were developed. Several cultures of the patient's specimen of blood, urine, sputum, and stool revealed no growth of any organisms including fungus. Following abdominal CT scan showed hepatosplenomegaly, decreased enhancement in both kidneys and 2 cm-sized cystic lesion in spleen.

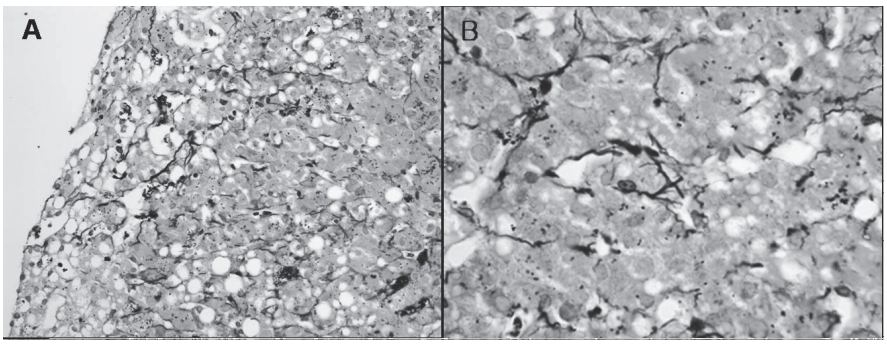

Fig. 1. Light microscopic exam of patient's liver biopsy. Multiple scattered yeasts and pseudohyphae are noted. (Grocott's methenamine silver stain, A: X 100, B: X 400).

Without evidence of other infection or fever focus, liver biopsy was taken for evaluating the reason for hepatic failure on the 20th hospital day. Typical yeast and pseudohyphae were found in the biopsy specimen (Fig. 1), and the diagnosis of hepatosplenic (chronic disseminated) candidiasis was confirmed.

Targeted treatment of chronic disseminated candidiasis was settled with amphotericin B, the total dose of the drug was 593mg, which was switched into liposomal amphotericin B due to renal insufficiency. Clinical features including fever and laboratory findings gradually improved. About 1 month after initiating amphotericin B, therapy has been maintained with oral fluconazole for 6 months.

Infection remains a major cause of morbidity and mortality in SLE (1, 2). Among those, opportunistic infections have been reported in 20% to 30% of patients' mortality (1, 3) and they are often problematic because they can mimic or be superimposed upon active lupus (4).

Chronic disseminated candidiasis (CDC) is seen typically in patients with leukemia who have received cytotoxic chemotherapy (5), but rarely reported in SLE. A combination of studies is often required and repeated examinations are warranted if the studies are negative initially, but the suspicion of CDC remains high. Modern radiologic tools are important in the early identification and management of the syndrome (6), but lesions cannot be detected by US, CT or MRI exam when the patient is neutropenic. Less than 20%-50% of patients with CDC are proven blood culture positive (5). Recent studies suggest that the detection of serum C-reactive protein, serum D-arabinitol (7), and serum beta-D-glucan (8) is useful for early suspicion of CDC. But none of these approaches has yet achieved widespread clinical acceptance and use. Amphotericin B deoxycholate has been the cornerstone of treatment of patients with CDC (9). Fluconazole (10) is an alternative choice for those patients who are stable and need prolonged therapy.

In summary, chronic disseminated candidiasis in SLE is a rare condition which has a very bad prognosis. A high index of suspicion for opportunistic infections like CDC, early and judicious diagnosis including tissue biopsy, and appropriate treatment would improve the prognosis of SLE patients.

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