Anti-Thyroid Autoantibody-Associated Interface Dermatitis in Individuals with Undifferentiated Connective Tissue Disease — An Unrecognized Subset of Autoimmune Disease?

WANLI CHENG, ANITA C. GILLIAM, ANTHONY CASTROVINCI, and MAHMOOD PAZIRANDEH

ABSTRACT. ***Objective.*** Skin conditions in individuals with undifferentiated connective tissue disease (UCTD) are poorly classified and characterized, and autoantibodies in serum can be heterogeneous and not always specific. We have identified a new subset of individuals with UCTD, interface dermatitis, and increased anti-thyroid antibodies.

Methods. We retrospectively reviewed 892 cases of individuals with UCTD. Serologic markers for CTD and autoantibodies against microsomes and/or thyroglobulin were analyzed. Skin lesions and medication history were documented, and persistent or recurrent skin lesions were biopsied.

Results. Anti-thyroid antibodies for thyroglobulin and/or microsomes (ATAb) were positive in 526 (59%). The ATAb(+) and ATAb(–) groups had similar antinuclear antibody (ANA) positivity (32% vs 28%, respectively), average age (59 vs 58 yrs), and female-male ratio (8:1 vs 6:1). ATAb positivity was significantly associated with a dermatitis manifested as erythematous macules/patches or papules on legs, upper arms, back, and shoulders in 9% (47/526) of ATAb(+) individuals versus 2% (7/366) in ATAb(–) individuals ($p < 0.0001$). Seventeen individuals with dermatitis, 15 ATAb(+) and 2 ATAb(–), had biopsies. Twelve biopsies (80%) from ATAb(+) individuals and one ATAb(–) individual showed a cell-poor lymphocytic interface dermatitis with vaculopathy of basal layer keratinocytes, dermal mucin deposition, and perivascular mononuclear inflammatory cell infiltrates in the upper dermis that spared eccrine glands. The interface dermatitis was not significantly associated with hypo- or hyperthyroidism, or medications.

Conclusion. We describe an ATAb-associated interface dermatitis in roughly 9% of ATAb(+) patients with UCTD, which may represent a new subset of autoimmune disease. ATAb may be a useful marker for some individuals with UCTD. (First Release Dec 15 2006; J Rheumatol 2006;34:81–8)

Key Indexing Terms:
UNDIFFERENTIATED CONNECTIVE TISSUE DISEASES INTERFACE DERMATITIS
DEFINED CONNECTIVE TISSUE DISEASE ANTI-THYROID AUTOANTIBODIES
ANTINUCLEAR ANTIBODIES

Connective tissue diseases (CTD) such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), dermatomyositis (DM), polymyositis (PM), systemic sclerosis (SSc), mixed connective tissue disease (MCTD), and primary Sjögren's syndrome (pSS) display a wide range of clinical manifestations and laboratory abnormalities. Several different sets of diagnostic criteria have been proposed for the CTD[1-10]. However, there is a distinct group of systemic disorders with signs and symptoms that have not yet developed sufficiently to allow classification by means of the generally accepted criteria[11-13]. These are now referred to as "undifferentiated connective tissue diseases" (UCTD). Whether the UCTD represent a distinct clinical entity characterized by specific clinical or immunological abnormalities, or the atypical delayed onset of some other well-defined clinical disease, is controversial[14-19]. In most cases the latter would occur in the first year of the disease course. Skin conditions in individuals with UCTD are common, but when they occur, they are poorly classified and not well characterized clinically or histologically. We studied skin conditions in 892 individuals with UCTD, and report an anti-thyroid antibody (ATAb)-associated interface dermatitis in some of these patients that may identify a new subset of autoimmune disease.

From the Department of Dermatology and Division of Rheumatology, Department of Internal Medicine, Case/University Hospitals of Cleveland, Cleveland, Ohio, USA.

W. Cheng, MD; A.C. Gilliam, MD, PhD; A. Castrovinci, MD; Department of Dermatology; M. Pazirandeh, MD, Division of Rheumatology, Department of Internal Medicine, Case/University Hospitals of Cleveland.

Address reprint requests to Dr. A. Gilliam, 529 BRB, Department of Dermatology, Case/University Hospitals of Cleveland, 11100 Euclid Avenue, Cleveland, OH 44106-5028. E-mail: anita.gilliam@case.edu

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MATERIALS AND METHODS

Patients. Between 1996 and 2004, 892 patients (female 784, male 108, age range 16–94 yrs) who had been referred to a rheumatologist (MP) were initially diagnosed as having a UCTD. The diagnosis of UCTD was based on the

following criteria: (1) the presence of clinical manifestations (including muscle weakness or muscle pain, arthralgia or arthritis, Raynaud's phenomenon, dry mouth, dry eyes, conjunctivitis, low grade fever, photosensitivity) suggestive of CTD; (2) the presence of at least one non-organ-specific autoantibody [antinuclear antibodies (ANA), anti-dsDNA antibodies, or anti-extractable nuclear antigen antibodies]; and (3) the absence of clinical, serological, or histological criteria to diagnose a specific CTD[12]. The patient selection criteria for this retrospective study were: (1) a diagnosis of UCTD, and (2) a followup of at least 1 year during which a definite CTD did not develop. Those patients whose disease subsequently evolved to an overt CTD within a year after initial diagnosis of UCTD were excluded from the study. Mosca, *et al* have suggested that a diagnosis of UCTD can be made if no other CTD can be diagnosed after 3 years[20]. However, most patients in that study who had not progressed after 1 year of symptom onset had not progressed after 10 years[20]. The second diagnosis was based on the American Rheumatism Association criteria for SLE[1], RA[7], and SSc[5]; Sharp's criteria for the diagnosis of MCTD[2,3]; the criteria of Vitali, *et al* for pSS[9,10]; and Bohan and Peter's criteria for PM-DM[8,21].

Other skin disorders such as exfoliative dermatitis, dermatitis herpetiformis, and dermatitis with gastrointestinal disease were excluded. The common comorbid conditions such as hypertension, coronary disease, and chronic pulmonary disease were deemed not to be important factors in this study.

The patient cohort was developed because of the observation by the rheumatologist (MP) that occasional patients with UCTD by the above criteria had positive ATAb. ATAb were then obtained for subsequent patients with UCTD and an unexplained dermatitis. These patients were then sent to a dermatologist (AC) for evaluation and skin biopsy.

Laboratory studies. Standard, validated techniques performed by reference laboratories routinely used by the rheumatologist were utilized[22]. ANA were first determined by screening with enzyme immunoassay (EIA). If positive (optical density > 1.5), then titer and reaction pattern were obtained by indirect immunofluorescence with HEp-2 cells and rat liver cells as antigen sources for the ANA test. Anti-dsDNA antibodies were determined by *Crithidia luciliae* assay. Enzyme immunoassay (EIA) was used to detect the anti-ENA antibodies (anti-SSA/Ro, anti-SSB/La, anti-RNP, anti-Sm, anti-Scl-70, anti-Jo-1, anti-Ku) and to detect antimicrosomal and antithyroglobulin antibodies. These laboratory data were obtained from standard reference laboratories routinely used by the primary physician (MP). Normal limits for each test were determined by these reference laboratories. In the case of ATAb, any value above the normal range (0–5 IU/ml) and in some cases 0–2 IU/ml by EIA for the reference laboratory for antimicrosomal was considered positive. For antithyroglobulin antibody, any value above that of the reference value (0–10 IU/ml) by EIA was considered positive. A positive reaction at 1:80 for ANA was considered a positive result. The serological testing was repeated at least once a year and in most instances 3 and 4 times in the course of followup. The data in the tables are the initial values.

Histology of skin biopsies. Skin specimens of a representative area of the erythematous patches/plaques were obtained by punch or shave-type biopsy by a dermatologist (AC) with informed consent, fixed in 10% buffered formalin, embedded in paraffin, and processed for routine hematoxylin and eosin staining. They were examined blinded by 2 dermatopathologists (AG and WC). In this retrospective analysis, direct immunofluorescence was not performed on biopsies from individuals with the interface dermatitis.

Medication history. Medications used before and during the followup period were documented in each patient's medical file kept in the rheumatology clinic. Medication history was reviewed to determine any potential relationship to the onset of skin lesions. The medical histories of 47 ATAb(+) UCTD patients with the dermatitis and those of a group of 59 ATAb(–) UCTD patients matched for sex, age, and disease duration without the interface dermatitis were analyzed and compared.

Statistical analysis. All variables were analyzed independently using the chi-square test or Fisher's exact test for 2 × 2 tables, as appropriate. Multivariate linear analysis was then used to identify those variables that could jointly represent a predictor of the skin disease.

RESULTS

Serological findings. A total of 892 consecutive patients diagnosed with UCTD who retained the diagnosis for 1 year were enrolled in the study between 1996 and 2004. Of them, 526 (59%) individuals were ATAb(+) (Table 1). Other major serological findings included 270 (30%) individuals who were ANA(+), 59 (7%) being SSA/Ro-positive and 29 (3%) SSB/La-positive. In addition, cryoglobulinemia was noted in 74 (8%) individuals. The major serological findings of the ATAb(+) and ATAb(–) groups are summarized in Table 1. As shown, no significant difference was observed between the 2 groups for ANA positivity and for SSA/Ro and SSB/La antibody positivity. The average age (59 vs 58 yrs) and female to male ratio (8:1 vs 6:1) were also similar in the ATAb(+) and ATAb(–) groups.

ATAb-associated skin lesions. During the followup period of 1 year or more, a total of 47 patients manifested one or more types of skin lesions or signs. The frequency of the major types of skin lesions or signs is summarized in Table 2. As shown, 3 skin conditions, dermatitis, chronic urticaria, and unexplained cutaneous edema of extremities and trunk, were associated with ATAb positivity. Other skin conditions found in individuals with UCTD included Raynaud's phenomenon (105/892, 12%), photosensitivity (53/892, 6%), psoriasis (54/892, 6%), panniculitis, vasculitis, and other unclassified skin lesions (23/892, 3%). These were similar in both ATAb(+) and ATAb(–) groups.

The dermatitis (Figure 1, representative patients a–f), typically erythematous macules/patches or papules on lower extremities, was found significantly more often in the

Table 1. Comparison of major serological findings in 892 individuals with UCTD.

	Total 892	ATAb(+) n (%) 526 (59)	ATAb(–) n (%) 366 (41)
ANA+	270 (30)	168 (32)	102 (28)
SSA+	59 (7)	32 (6)	27 (7)
SSB+	29 (3)	16 (3)	13 (4)
Cryoglobulins+	74 (8)	44 (8)	30 (8)

Table 2. Skin conditions in individuals with UCTD (n = 892).

	ATAb(+) n = 526 (%)	ATAb(–) n = 366 (%)
Dermatitis*	47 (9)	7 (2)
Chronic urticaria	12 (2)	0 (0)
Unexplained edema	15 (3)	1 (0.3)
Raynaud's phenomenon	71 (14)	34 (9)
Photosensitivity	29 (6)	24 (7)
Psoriasis	26 (5)	28 (8)
unclassified	17 (3)	6 (2)

* $p < 0.0001$

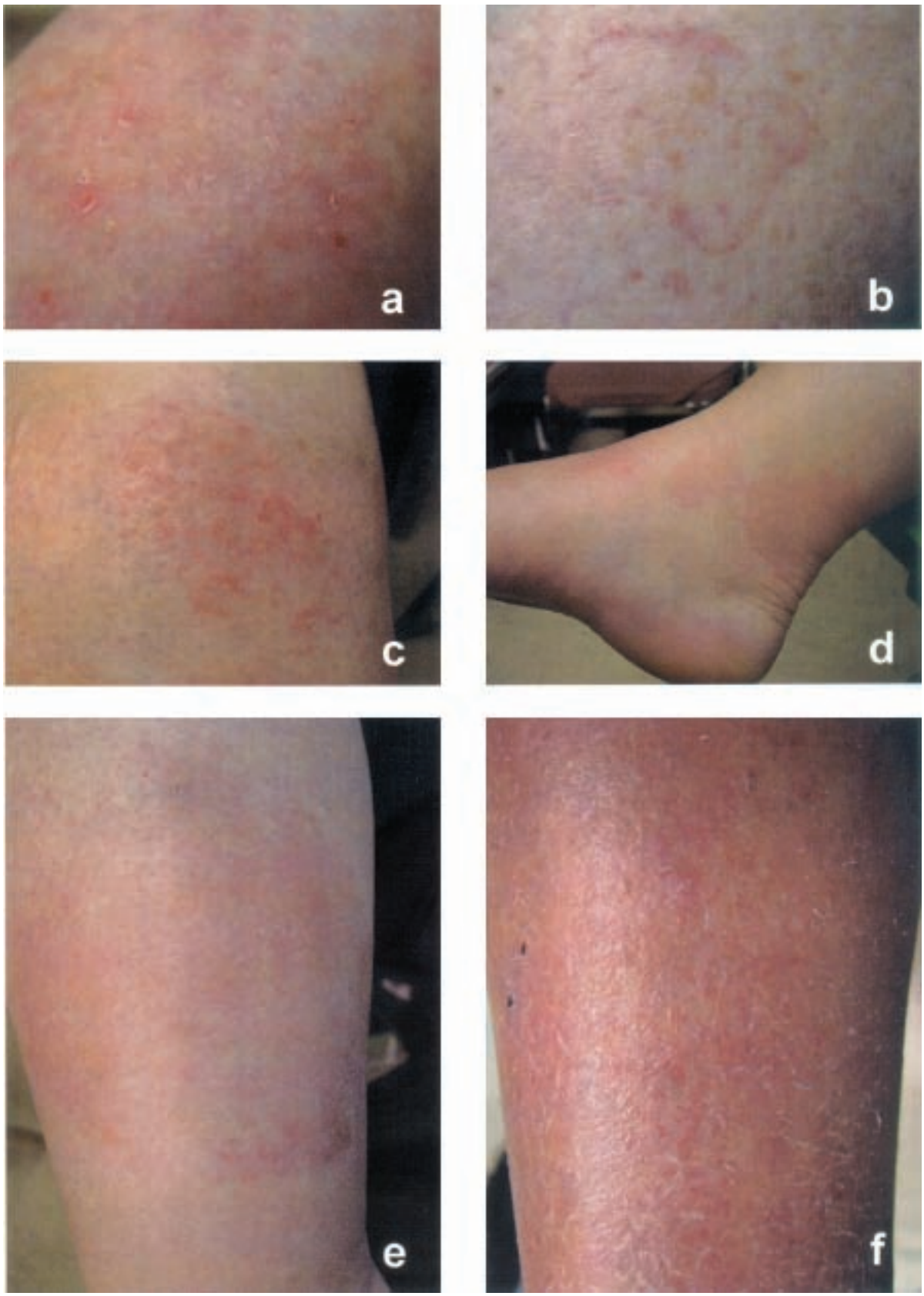

Figure 1. Skin lesions in representative patients with anti-thyroid antibodies and undifferentiated connective tissue disease. Erythematous macules, papules, or patches with delicate scale are shown on shoulders and arms (a–c). The skin lesions are most commonly found on lower extremities (d–f).

ATAb(+) group (47/526, 9%) than in the ATAb(–) group (7/366, 2%) (Table 2; Pearson's chi-square = 18.7, $p < 0.0001$). The locations of the patients' lesions were as follows: 26 on lower extremities, 8 on upper extremities, 8 on trunk (shoulders and back), 2 on face, 2 on scalp, and one on gums. As can be seen in Figure 1, these skin lesions resemble systemic or subacute cutaneous lupus erythematosus (SCLE).

A less prominent but statistically significant association between the dermatitis and ANA positivity was also noted (Pearson's chi-square = 5.089, $p < 0.024$). However, the dermatitis was not significantly associated with anti-SSA/Ro and/or anti-SSB/La autoantibodies (Table 3). Anti-DNA antibodies (Sm, RNP, anti-dsDNA) were not tested on the group of ANA(+) individuals (23/47). The presence of a positive anti-DNA antibody would not have changed our diagnosis of UCTD in this subset of patients with incomplete criteria for

Table 3. Serological profiles of 47 individuals with UCTD and an ATAb-associated dermatitis.

Case	Age/Sex	ANA	Anti-thyroglobulin (titers) IU/ml	Anti-microsome (titers) IU/ml	Ro/SSA	La/SSB	Followup, mo
5	72/F	+	+ (7)	+ (71)	–	–	50
189	45/F	+	–	+ (34)	–	–	61
197	82/F	+	+ (327)	–	ND	ND	52
210	34/F	+	–	+ (169)	–	–	28
234	59/F	+	–	+ (16)	+	–	14
236	47/F	+	–	+ (25)	–	–	30
277	66/F	+	+ (85)	+ (63)	–	–	61
281	59/M	+	+ (12)	+ (39)	–	–	18
300	46/F	+	+ (36)	–	–	–	61
322	52/F	+	+ (196)	+ (17)	+	–	19
443	54/F	+	–	+ (71)	–	–	16
464	49/F	+	+ (28)	+ (71)	–	–	36
534	65/F	+	—	+ (71)	+	–	61
545	51/F	+	+ (31)	+ (71)	–	–	61
571	46/F	+	–	+ (12)	–	–	61
621	43/F	+	+ (91)	+ (71)	–	–	20
710	42/F	+	–	+ (25)	+	+	14
944	43/F	+	+ (148)	+ (6)	–	–	61
1022	45/F	+	+ (27)	+ (67)	–	–	12
1043	79/F	+	+ (60)	+ (34)	–	–	24
1071	55/F	+	+ (91)	+ (71)	–	–	16
3001	47/F	+	+ (90)	+ (70)	–	–	46
3002	52/F	+	ND	+ (20)	+	–	23
88	38/M	–	+ (65)	+ (36)	–	–	23
92	49/F	–	–	+ (71)	–	–	30
123	78/F	–	+ (25)	+ (16)	–	–	12
170	51/F	–	+ (199)	+ (104)	–	–	52
237	51/F	–	+ (25)	+ (62)	–	–	61
239	39/M	–	+ (26)	–	–	–	16
246	67/F	–	–	+ (53)	–	–	61
261	59/F	–	+(91)	+ (71)	ND	ND	17
282	61/F	–	+ (15)	–	–	–	61
290	71/F	–	–	+ (70)	–	–	12
307	40/F	–	–	+ (370)	–	–	18
311	88/F	–	–	+ (7)	–	–	25
530	83/F	–	—	+ (5)	–	–	40
600	35/F	–	–	+ (617)	–	–	23
773	65/F	–	–	+ (8)	–	–	50
780	86/F	–	+ (25)	+ (73)	ND	ND	61
881	46/F	–	–	+ (71)	–	–	30
941	45/F	–	+ (12)	+ (71)	–	–	30
968	30/F	–	+ (28)	–	–	–	30
987	66/M	–	+ (19)	+ (6)	–	–	20
1001	59/F	–	+ (46)	+ (359)	–	–	14
1074	74/F	–	–	+ (193)	–	–	18
3003	67/F	–	+ (1065)	–	+	–	61
3004	69/M	–	–	+ (4)	–	–	12

F: female, M: male, (+): positive, (–): negative, ND: not determined.

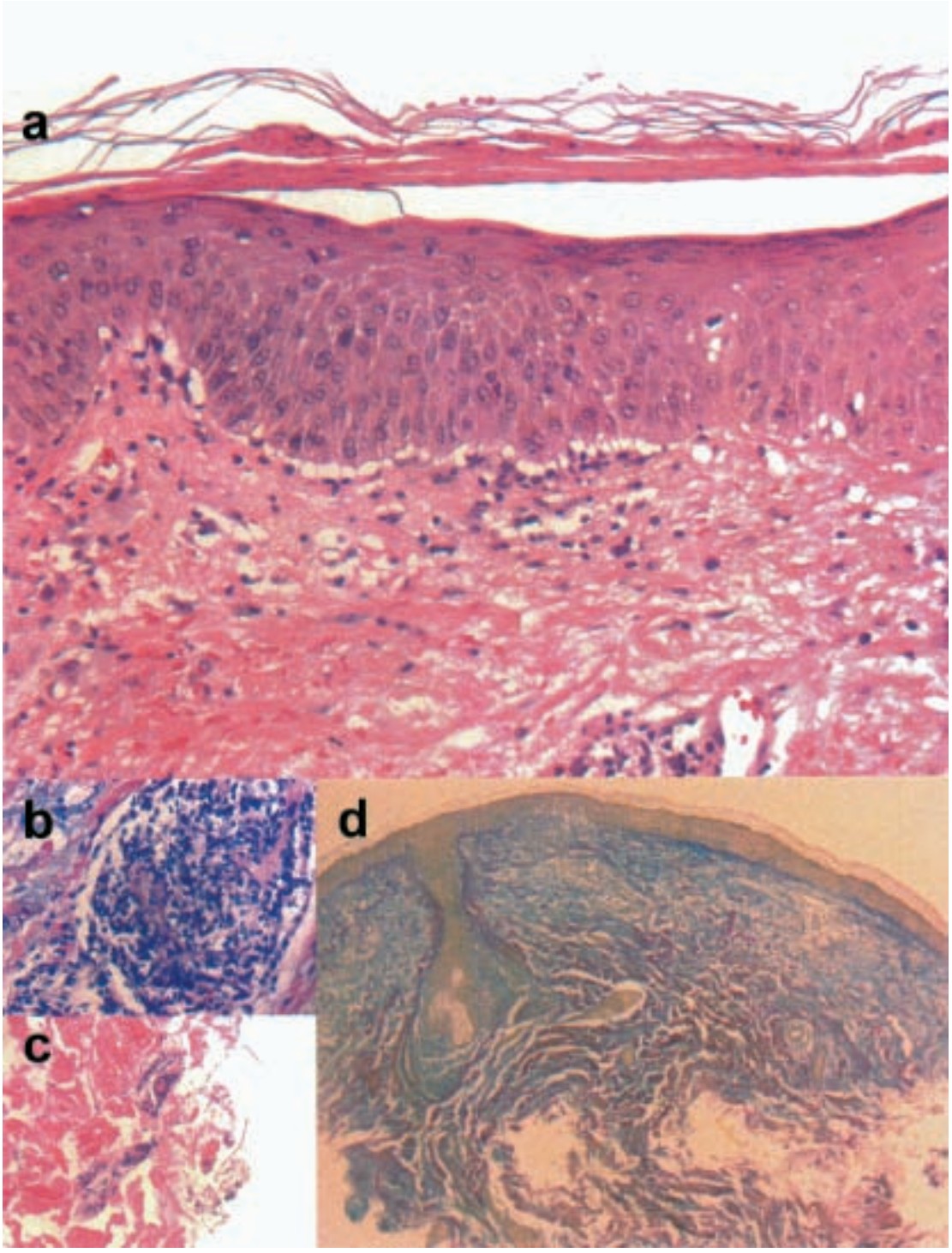

Figure 2. Histology of selected skin biopsies (n = 14) of individuals with ATAb-associated dermatitis. A. There is a cell-poor lymphocytic interface reaction with prominent vaculopathy of epidermis, seen as bubbly appearance at the epidermal-dermal junction where lymphocytes (small dark nuclei) tag the basal layer of keratinocytes. Hyperkeratosis correlates with the scale seen clinically. The dermal inflammatory infiltrates are mononuclear cells; eosinophils are rarely found. Extravasated red blood cells are present in the lower left corner of the micrograph (H&E, 40×). B. The dermal infiltrates of lymphocytes and histiocytes involve superficial vessels (H&E, 20×). Extravasated red blood cells are often seen around the vessels (not shown). C. The dermal infiltrates spare eccrine glands (H&E, 20×). Involvement of eccrine glands is a histological clue for systemic and discoid lupus erythematosus. D. Mucin is present at all levels of dermis, seen in colloidal iron-stained sections as teal-blue material between the pink collagen bundles (10×). The vaculopathic changes of epidermis are not as apparent at this magnification, but can be seen at higher power (not shown).

SLE. Seventeen persistent or recurrent skin lesions resistant to topical treatments were biopsied, 15 from ATAb(+) and 2 from ATAb(–) individuals.

Histopathological findings. On microscopic examination of H&E-stained tissue sections, 12 of 15 (80%) biopsies from ATAb(+) individuals showed a cell-poor lymphocytic interface dermatitis with prominent basal layer vaculopathy of keratinocytes, and a mild to moderate perivascular lymphocytic infiltrate admixed with variable histiocytes in the superficial dermis (representative histology Figures 2a and 2b). Inflammatory infiltrates typically spared cutaneous adnexal structures (Figure 2c). Involvment of adnexae is a clue to CTD such as systemic and discoid lupus erythematosus. Lymphocytic vasculopathy was visible in which red blood extravasation was seen around superficial dermal vessels that were surrounded by dense lymphohistiocytic infiltrates in some of these cases (Figure 2a). Rare eosinophils were noted in the infiltrate in one case. Mild to moderate, patchy to diffuse dermal mucin deposition was observed in all 12 biopsies with interface dermatitis. The dermal mucin deposition was highlighted and confirmed by colloidal iron staining (Figure 2d). This histology most closely resembles SCLE or DM in the subtle interface dermatitis, dermal mucin deposition, and sparse or absent periadnexal inflammatory infiltrates. One biopsy from the ATAb(–) group showed a similar interface dermatitis. The serological profile for the 17 individuals with a skin biopsy is summarized in Table 4.

Medication history. To determine whether the interface dermatitis was associated with medication use, the medications of the 47 individuals with UCTD, a positive ATAb, and the interface dermatitis were reviewed and compared with those of 59 age, sex, and UCTD disease length-matched individuals who were ATAb(–) and did not have a dermatitis. The medications commonly used in both groups of patients are listed in Table 5. They included nonsteroidal antiinflammatory drugs (NSAID), plaquenil, thyroid hormone, estrogen/progestin, and methotrexate (> 10%), acetaminophen, and bisphosphonate (< 10%) in the ATAb(+) group. As shown, 19 (40%) individuals who had the ATAb-associated dermatitis had been taking thyroid hormone-replacement therapy as compared with 6 (10%) in the matched ATAb(–) individuals ($p < 0.01$). However, with thyroid hormone-replacement therapy, all 19 individuals maintained normal thyroid function clinically and normal serum thyroid-stimulating hormone levels during the study period (data not shown). In contrast, NSAID were used significantly more frequently in the matched ATAb(–) individuals than in the individuals who were ATAb(+) and had the interface dermatitis. Therefore there was a negative association of positive ATAb, dermatitis, and NSAID use. No significant difference in frequency of using other commonly used medications was noted in both groups of individuals.

DISCUSSION

We identified 47 cases (approximately 9%) in our study of 526 individuals who had an interface dermatitis, ATAb (antithyroglobulin and/or anti-microsome), and clinical symptoms of UCTD in a total of 892 individuals with UCTD. The skin disease consisted of erythematous macules, patches, or papules with delicate scale, found most frequently on thighs, lower legs, upper arms, upper back, and shoulders, in that order (Figure 1). Skin biopsies in 15 of 47 of these individuals (Figure 2) all showed mild lymphocyte-poor interface der-

Table 4. Serological profiles and biopsy results of 17 individuals with UCTD and dermatitis.

Case	ANA	Anti-thyroglobulin 0–10 IU/ml normal	Anti-microsome 0–5 IU/ml normal	Ro/SSA	La/SSB	Pathology Diagnosis
5	+ (80 homo)	—	+ (71)	–	–	Interface, LCV
170	–	+ (199)	+ (104)	–	–	Interface
239	–	+ (26)	–	–	–	Interface
281	+ (640 homo)	+ (12)	+ (39)	–	–	Interface
290	–	–	+ (70)	–	–	Interface
307	–	–	+ (370)	–	–	Lichenoid/interface
443	+	–	+ (71)	–	–	Vasculopathy
534	+ (80 spkl)	—	+ (71)	+	–	Interface
545	–/+ (40 spkl)	+ (31)	+ (71)	–	–	Nonspecific
773	–	–	+ (8)	–	–	Granuloma annulare
791	–/+ (40 nucl)	–	–	+	–	Scar
896	–	ND	–	–	–	Interface
1071	+	+ (91)	+ (71)	–	–	Interface
1074	–	–	+ (193)	–	–	Interface
3002	+ (640 spkl)	ND	+ (20)	+	–	Interface
3003	–	+ (1065)	–	+	–	Interface
3004	–	–	+ (4)	–	–	Interface

LCV: leukocytoclastic vasculitis, homo: homogeneous; spkl: speckled; nucl: nucleolar.

Table 5. Comparison of medication history in age, sex, and disease duration-matched individuals with UCTD.

	ATAb(+) with dermatitis n = 47 (%)	ATAb(–) without dermatitis n = 59 (%)
** NSAIDS	20 (43)	40 (68)
Plaquenil	13 (28)	20 (34)
* Thyroid hormone	19 (40)	6 (10)
Estrogen/progestin	8 (17)	4 (7)
Methotrexate	6 (13)	11 (19)
Acetaminophen	3 (6)	10 (17)
Bisphosphonate	3 (6)	10 (17)

* $p < 0.01$, $\chi^2 = 6.786$; ** $p < 0.001$, $\chi^2 = 13.288$.

matitis with vaculopathy of basal keratinocytes, superficial perivascular infiltrates of mononuclear inflammatory cells that spared eccrine glands, patchy dermal mucin, and occasional lymphocytic vasculopathy. To our knowledge, ours is the first report of this association.

We considered the possibility that the dermatitis could represent SCLE, which in elderly patients can be triggered by drug therapy, especially thiazides and calcium channel blocking agents[23-25]. However, the dermatitis appeared not to be related to medications (Table 5) and the distribution predominantly on the lower extremities was unusual for SCLE or SCLE-like drug reaction, which typically involves sun-exposed areas such as shoulders, arms, and back. Further, the onsets and/or fluctuations of the dermatitis appeared not to be related to starting or stopping of medications (data not shown). The low serological positivity rates for anti-SSA/Ro (13%) and anti-SSB/La (2%) in this group of patients (Table 4) also argues against the possibility that the dermatitis represents SCLE, which occurs in 75–90% of individuals with these autoantibodies[26,27]. We speculate that the ATAb positivity is the result of these individuals with UCTD having an autoimmune process in which ATAb autoantibodies are produced nonspecifically by a dysregulated immune system. We did not test for other autoantibodies that would not be detected by ANA testing.

ATAb are one of the most common autoantibodies in the general population (about 10–14% of asymptomatic individuals have ATAb). ATAb are also found in the CTD[28], again suggesting a nonspecific dysregulation of the immune system.

In summary, ATAb testing may be useful in identifying a subset of individuals with UCTD that do not have thyroid dysfunction. Nine percent of these individuals can have a characteristic dermatitis that resembles SCLE or DM histologically, but is seen predominantly in the lower extremities rather than the shoulders and arms and is not associated with SSA/Ro or SSB/La autoantibody positivity. ATAb testing may be another useful marker for UCTD and is significantly associated with a characteristic dermatitis. Although we have no evidence for this hypothesis, we can speculate that the combination of ATAb and interface dermatitis may predict progression ultimately to one of the CTD, such as lupus erythematosus or DM, with similar skin disease.

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