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Association and Similarities between Undifferentiated Connective Tissue Diseases and Autoimmune Thyroid Diseases

Undifferansiye Bağ Doku Hastalıkları ve Otoimmün Tiroid Hastalıklarının Birlikteliği ve Benzerlikleri

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Abstract

Objectives: Autoimmune thyroid diseases (ATDs) can be accompanied by systemic autoimmune diseases. The aim of this study was to determine the association, similarities, and differences between undifferentiated connective tissue diseases (UCTDs) and ATDs.

Materials and Methods: Fifty-nine UCTD patients and 108 control subjects were retrospectively evaluated. Thyroid function tests, antithyroid antibodies, antinuclear antibody (ANA), anti-double stranded deoxyribonucleic acid and anti-extractable nuclear antigens peptide levels, and histopathological examination of the minor salivary gland were evaluated.

Results: The prevalence of ATD was 23.70% and 33.30% in the UCTD and control groups, respectively (p = 0.220). The prevalence of arthritis in isolated UCTD patients was 11.10%, which was significantly increased (35.70%) if UCTD was accompanied by a ATD (p = 0.047). Other clinical symptoms such as arthralgia, xerostomia, keratoconjunctivitis sicca, Raynaud's phenomenon, oral aphthous ulcers, and photosensitivity observed in UCTD, ANA positivity rates, and the most common staining pattern (speckled) were similar between the ATD and non-ATD patients. Histopathological examination of the minor salivary gland in 9 ATD patients revealed no significant lymphocyte infiltration. In the comparison of UCTD and ATD patients, the findings were similar, except arthralgia and ANA positivity, which were higher in UCTD patients.

Conclusion: As a result, considering similar clinical symptoms and autoimmune profiles of UCTD and ATD, it is recommended to make a clear differential diagnosis of both diseases in patients presenting with complaints such as arthralgia, xerostomia, and Raynaud's phenomenon.

Keywords: Undifferentiated connective tissue disease, autoimmune thyroid disease, antithyroid antibodies, antinuclear antibody

Öz

Amaç: Otoimmün tiroid hastalıkları (OTH) sistemik otoimmün hastalıklara eşlik edebilmektedirler. Bu çalışmanın amacı Undifferansiye Bağ Doku Hastalıkları (UBDH) ve OTH hastalıkları arasındaki ilişkiyi, benzerlikleri ve farklılıkları saptamaktır.

Materyal ve Metot: Çalışmaya 59 UDBH hastası ve 108 kişilik kontrol grubu alındı. Tiroid fonksiyon testleri, antitiroid antikorları, antinükleer antikorlar (ANA), anti-dsDNA ve ekstrakte edilebilen nükleer antijenlere karşı gelişen antikorların seviyeleri ile minör tükürük bezinin histopatolojik incelemesi değerlendirildi.

Bulgular: OTH prevalansı UDBH grubunda %23,70, kontrol grubunda ise %33,30 olarak bulundu (p=0,220). İzole UDBH'da artrit görülme oranı %11,10 iken, OTH ile birlikteliği durumunda bu oranın %35,70 olarak anlamlı derecede artmış olduğu saptandı (p=0,047). UDBH da görülen artralji, xserostomi, keratokonjuktivitis sikka, raynaud, oral aft ve fotosensitivite gibi diğer klinik belirtiler, ANA pozitiflik oranları ve en sık görülen boyanma paterni benekli olmak üzere OTH olan ve olmayanlarda benzerdi. OTH bulunan 9 hastanın yapılan minör tükürük bezinin histopatolojik incelemesinde anlamlı bir lenfosit infiltrasyonu izlenmedi. Tek başına UDBH ile OTH olan hastalar karşılaştırıldığında, UDBH'da daha yüksek oranda görülen artralji ve ANA poziftiliği dışında diğer bulgular benzerdi.

Sonuç: Sonuç olarak, UDBH ile OTH klinik belirtileri ve otoimmün profilinin büyük oranda benzer olduğu göz önüne alınarak artralji, xserotomi, raynaud gibi yakınmalar ile gelen hastalarda her 2 hastalığın ayırıcı tanısının iyi yapılması ve ayrıca bu iki hastalığın birlikte bulunabileceğinin de göz önünde tutulması önerilir.

Anahtar Kelimeler: Undiferansiye bağ doku hastalığı, otoimmün tiroid hastalığı, antitiroid antikor, antinükleer antikor

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Introduction

Autoimmune diseases develop due to inappropriate responses of the immune system to its own cells, tissues, and/or organs. Although these diseases can be localized to a single organ or tissue, they can also be associated with systemic involvement by affecting more than one tissue and organ.

Autoimmune thyroid diseases (ATDs) are predominantly characterized by B and T lymphocyte infiltration of the thyroid gland in association with immune system dysregulation. The most common ATDs among organ-specific autoimmune diseases can be accompanied by systemic autoimmune diseases, such as Sjögren's syndrome (SS), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE).[1-3] ATDs are characterized by the emergence of specific antibodies to thyroglobulin, thyroid peroxidase, or thyrotropin receptor autoantigens.[4] In addition, non-thyroid-specific antibodies, such as antinuclear antibody (ANA), anti-double-stranded deoxyribonucleic acid (anti-dsDNA), and anti-extractable nuclear antigens (anti-ENA), are positive in ATDs.[5]

Although organ-specific autoimmune diseases often have an effect on a single organ or tissue, their clinical effects are often reflected in other organs and systems. Rheumatic symptoms such as osteoarthritis, carpal tunnel syndrome, myopathy, polyarthralgia, non-inflammatory arthropathy, and inflammatory arthritis may also be observed in ATDs.[6-9]

The term “undifferentiated connective tissue disease (UCTD)” is used to describe a condition with clinical and serological findings that indicate a systemic autoimmune disease but that do not meet the classification criteria of a defined connective tissue disease. The most common symptoms of UCTD are arthralgia (37%–80%), arthritis (14%–70%), Raynaud’s phenomenon (45%–60%), leukopenia (11%–42%), xerostomia (7%–40%), and keratoconjunctivitis sicca (8%–36%). Although ANA positivity is not a must for the diagnosis of UCTD, it was shown to be present in 58%–100% of patients. The most common autoantibodies in UCTD other than ANA are anti-Ro/SSA (8%–30%) and anti-RNP (10%–30%).[10]

ATD and UCTD have common clinical symptoms and findings, such as arthralgia, arthritis, xerostomia, and ANA positivity. The aim of this study, which was planned as a retrospective study, was to compare clinical data of patients admitted to the rheumatology outpatient clinic and diagnosed with UCTD and ATD after the examinations and consequently to determine similarities and differences between these diseases.

Materials and Methods

Patients

Patients aged ≥18 years who were voluntarily admitted to the rheumatology outpatient clinic of the Antalya Training and Research Hospital or for whom a consultation was requested by other departments between 2010 and 2017 were evaluated. Following an evaluation of patients who were not diagnosed with any rheumatic disease, those who did not meet any criteria for a specific autoimmune disease despite the presence of at least one clinical symptom (such as arthralgia, xerostomia, or Raynaud's phenomenon) suggesting a connective tissue disease for >3 years, and ANA (IFA) and/or anti-ENA positivity were considered as UCTD and enrolled in the study.[11] Among patients whose ANA (IFA) and/or anti-ENA antibodies were analysed, those who were not diagnosed with any rheumatic disease and those who did not meet the criteria for UCTD were enrolled as the control group.

All patients were screened for free T3 (fT3), free T4 (fT4), thyroid-stimulating hormone (TSH), anti-thyroid peroxidase (anti-TPO) and/or anti-thyroglobulin (anti-TG) levels, thyroid imaging and/or histopathological evaluation, and levothyroxine/antithyroid therapies received. The diagnosis of ATD is made according to established criteria based on thyroid hormone levels, serum antibodies against thyroid antigens (anti-TPO and/or anti-TG) and thyroid examination.

Patients diagnosed with any rheumatic diseases, such as SLE, SS, and RA; those with a chronic systemic disease, such as renal failure; and those with a history of malignancy or thyroid surgery were excluded.

Clinical and laboratory evaluation

In laboratory tests conducted, hemogram, C reactive protein, fT3, fT4, TSH, anti-TPO, anti-TG, rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), ANA (IFA), anti-ENA, anti-dsDNA, complement 3 (C3), and complement 4 (C4) levels were evaluated.

Serum TSH, fT3, fT4 and antithyroid autoantibodies levels were analysed with chemiluminescence immunoassay using commercially available assay kits (Beckman Coulter) and an AutoAnalyzer (Access DxI800; Beckman Coulter Diagnostics). Positive values for the anti-TPO and anti-TG were >5 and >10 IU/mL, respectively.

ANAs were detected by indirect immunofluorescence on HEp-2 cells (Euroimmun, Lubeck, Germany) at a screening dilution of 1:100. Fluorescent acuity was determined semiquantitatively based on negative control (-) and positive control (+4) ranging from +1 to +5. A subgroup of patients and controls was further tested at dilutions of 1:320 and 1:1000. Antibodies to the extractable nuclear antigens [uridine 1-low-molecular-weight ribonuclear protein (nRNP), Smith antigen (Sm), soluble substance A (SSA native and Ro 52), soluble substance B (SS-B), DNA topoisomerase I (Scl-70), cytoplasmic histidyl-tRNA synthetase (Jo-1), centromeres (CENP B), proliferating cell nuclear antigen (PCNA), dsDNA, nucleosomes, histones, ribosomal P-protein (RibPP), and pyruvate dehydrogenase complex including antimitochondrial M2 antigens (AMA-M2)] were determined by using the ANA profile 3 kit (Euroline, Euroimmun). RF was detected with a commercially available kit (N Latex RF kit, Siemens Diagnostics, Marburg, Germany).

In addition, biopsies obtained from the minor salivary gland for diagnostic purposes were evaluated, when required. Histopathological analyses of the minor salivary gland biopsy samples were assessed using the Chisholm classification.[12]

The study was approved by the Ethics Committee of the Akdeniz University Faculty of Medicine.

Statistical analysis

SPSS package software (Version 22, SPSS Inc., Chicago, IL) was used for statistical analysis. Continuous data were expressed as mean ±SD, whereas categorical variables were expressed as percentages. Student's t-test was used in comparison the means of two independent samples. Chi-square test was used to analyse categorical variables. The values of $p < 0,05$ were considered as statistically significant.

Results

The study included 59 UCTD patients (54 women, 5 men; age range: 18–76 years) and 108 control subjects (104 women, 4 men; age range: 19–68 years). Demographic, clinical, and laboratory characteristics of patients are presented in Table 1. There was no significant difference between the groups in terms of sex and mean age. The frequency of arthritis and dry mouth was significantly higher in the UCTD group than the control group, while arthralgia was higher in the control group. And there were no significant differences between the groups in terms of the frequency of the dry eyes, oral aphthous ulcers, Raynaud's phenomenon, and photosensitivity. Majority of the patients in both groups -55 (93.20%) in the UCTD group and 85 (78.70%) in the control group- were euthyroid. Three euthyroid patients in the UCTD group and 11 patients (7 with euthyroidism and 4 with hypothyroidism) in the control group had been treated with L-tyhroxine. The prevalence of ATD was 23.70% and 33.30% in the UCTD and control groups, respectively, and there was no significant difference between both groups. The rate of RF positivity (autoantibodies not specific to any organ) was similar in both groups, whereas ANA positivity was significantly higher in the UCTD group (Table 1).

The most common ANA staining patterns were speckled (49.20%), nucleolar (25.40%), and homogeneous (13.60%) in the UCTD group and speckled (18.50%) and nuclear dense fine speckled (13.90%) in the control group (Table 1). Anti-CCP test was studied in 34 patients (17 UCTD patients and 17 control subjects). The results were negative in all patients (data not shown). There was no significant difference between the UCTD and control groups in terms of CRP, C3, and C4 levels.

The frequency of clinical symptoms in patients with euthyroidism and hypothyroidism was similar in both UCTD and control groups (data not shown). The comparison of patients with euthyroidism and hyperthyroidism in the control group revealed that only oral aphthous ulcers were more common in patients with hyperthyroidism.

A total of 12 patients -10 UCTD patients and 2 control subjects- had arthritis. Among these patients, a total of 11 patients (2 control subjects and 9 UCTD patients) were euthyroid and 1 UCTD patient had hypothyroidism. In addition, among UCTD patients, the prevalence of arthritis was significantly higher in patients with ATD (35.70%) than those with non-ATD (11.10%), whereas in the control group, it was similar in patients with ATD and non-ATD (Table 2).

Table 1. Demographic, clinical and laboratory features of UCTD patients and control group

	UCTD patients (n=59)	**Control group (n=108)**	**P**
Age, years, mean ±SD	42.70±12.30	42.50±11.30	0.904
Gender (female), (%)	54 (91.50)	104 (96.30)	0.281
Clinical features, (%)			
Arthralgia	46 (78)	53 (49.10)	<0.001
Arthritis	10 (16.90)	2 (1.90)	0.001
Xerostomia	31 (52.50)	34 (31.50)	0.012
Keratoconjunctivitis sicca	24 (40.70)	33 (30.60)	0.232
Oral aphthous ulcers	9 (15.30)	14 (13)	0.815
Raynaud's phenomenon	4 (6.80)	8 (7.40)	1.000
Photosensitivity	2 (3.40)	3 (2.80)	1.000
Thyroid function, (%)			
Euthyroid	55 (93.20)	85 (78.70)	0.015
Hypothyroid	4 (6.80)	13 (12)	0.283
Hyperthyroid	0	10 (9.30)	0.016
Thyroid autoantibodies, (%)			
Anti-TPO	14 (23.70)	31 (28.70)	0.585
Anti-Tg	7 (12.30)	22 (21.20)	0.201
Total	14 (23.70)	36 (33.30)	0.220
ANA positivity (%)	56 (94.90)	49 (45.40)	<0.001
ANA pattern, (%)			
Nuclear speckled	29 (49.20)	20 (18.50)	<0.001
Nucleolar	15 (25.40)	6 (5.60)	
Homogenous	8 (13.60)	4 (3.70)	
Dense fine speckled	1 (1.70)	15 (13.90)	
Nuclear envelope	2 (3.40)	1 (0.90)	
Nuclear dot	1 (1.70)	3 (2.80)	
RF positivity, (%)	4/57 (7)	2/106 (1.90)	0.185
CRP, mean ±SD	3.53±5.71	2.29±4.03	0.105
C3, mean ±SD	1.16±0.30	1.22±0.34	0.323
C4 mean ±SD	0.91±3.99	0.25±0.08	0.198

UCTD, undifferentiated connective tissue diseases; SD, standart deviation; anti-TPO, anti-thyroid peroxidase antibody; anti-Tg, anti-thyroglobulin antibody; ANA, antinuclear antibody; RF, rheumatoid factor; CRP, C-reactive protein; C3, complement 3; C4, complement 4.

Other clinical symptoms and ANA positivity rates were similar in patients testing positive and those testing negative for antithyroid antibodies in both groups (Table 2). Staining patterns were not affected by antithyroid antibody positivity in both groups. Among UCTD patients who had ATD, 2 (14.30%) and 1 (7.10%) of 14 patients tested positive for anti-SSA and anti-Ro-52, respectively, whereas among 29 subjects in the

control group, 1 (3.40%) tested positive for anti-SSA, 1 (3.40%) for Ku, 1 (3.40%) for DFS-70. 1 (3.40%) for AMA, and 1 (3.40%) for PCNA.

Table 2. Comparison of clinical features and ANA pattern in UCTD patients and control group with and without ATD

	UCTD patients (n=59)			**Control group (n=108)**		
	ATD (+) (n=14)(%)	**ATD (-) (n=45)(%)**	***p***	**ATD (+) (n=36)(%)**	**ATD (-) (n=72)(%)**	***p***
Clinical features (%)						
Arthralgia	12 (85.70)	34 (75.60)	0.713	18 (50)	35 (48.60)	0.892
Arthritis	5 (35.70)	5 (11.10)	0.047	1 (2.80)	1 (1.40)	1.000
Xerostomia	8 (57.10)	23 (51.10)	0.766	15 (41.70)	19 (26.40)	0.107
KS	8 (57.10)	16 (35.60)	0.131	11 (30.60)	22 (30.60)	1.000
OAU	1 (7.10)	8 (17.80)	0.311	6 (16.70)	8 (11.10)	0.418
RP	2 (14.30)	2 (4.40)	0.236	5 (13.90)	3 (4.20)	0.069
Photosensitivity	1 (7.10)	1 (2.20)	0.421	2 (5.60)	1 (1.40)	0.257
ANA positivity, (%)	13 (92.90)	43 (95.60)	0.564	19 (52.80)	30 (41.70)	0.310
ANA pattern, (%)						
Nuclear speckled	9 (69.20)	20 (48.90)	0.544	8 (22.20)	12 (16.70)	0.331
Nucleolar	3 (23.10)	12 (26.60)		1 (2.80)	5 (6.90)	
Homogenous	-	8 (17.80)		2 (5.60)	2 (2.80)	
Dense-fine speckled	-	1 (2.30)		7 (19.40)	8 (11.10)	
Nuclear envelope	1 (7.70)	1 (2.30)		1 (2.80)	0	
Nuclear dot	-	1 (2.30)		0	3 (4.20)	

UCTD, undifferentiated connective tissue diseases; ATD, autoimmune thyroid disease; KS, Keratoconjunctivitis sicca; OAU, Oral aphthous ulcers; RP, Raynaud's phenomenon; ANA, antinuclear antibody

Salivary gland biopsy was performed in 21 UCTD patients and 9 control subjects. Among UCTD patients, the focus score (FS) was 0 in 20 patients and 1 in 1 patient, whereas it was 0 in all control subjects. One UCTD patient with an FS of 1 had no ATD, whereas 7 of 20 UCTD patients with an FS of 0 had ATD. In the control group, only 2 of 9 patients had ATD. Demographic characteristics of ATD patients for whom salivary gland biopsy results were available are presented in detail in Table 3.

In addition, similarities and differences between the characteristics of UCTD and ATD patients are presented in detail in Table 4.

In the control group, 1 patient had interstitial lung disease, 1 had livedo reticularis, 2 had fibromyalgia syndrome, and 2 had deep vein thrombosis of undefined etiology. The patient with interstitial lung disease had no clinical findings and/or non-organ-specific autoantibody positivity suggestive of a systemic autoimmune disease but had

hypothyroidism associated with Hashimoto's thyroiditis. Two patients diagnosed with fibromyalgia syndrome had hypothyroidism associated with Hashimoto's thyroiditis. The patient with livedo reticularis had only anti-TPO positivity but tested negative for all other autoantibodies.

Table 3. Clinical and serological features of nine patients with salivary gland biopsy

Patients	Sex/ Age	Clinical features	Schirmer test	ATA, serum levels (IU/mL)	ANA pattern	Anti-ENA	RF	F/G
UCTD	F/42	Arthritis, xerostomia, Raynaud's phenomenon	>5 mm	Anti-TPO, 964 Anti-Tg, 199	Nucleolar	Negative	Negative	0/0
UCTD	F/42	Xerostomia	>5 mm	Anti-TPO, 193 Anti-Tg, 424	Speckled	Anti-SSA	Negative	0/1
UCTD	F/55	Keratoconjunctivitis sicca, xerostomia	<5 mm	Anti-TPO, 592 Anti-Tg, 19.8	Speckled	Negative	Negative	0/1
UCTD	F/39	Arthralgia, xerostomia, Raynaud's phenomenon	>5 mm	Anti-TPO, 40.7 Anti-Tg, 95.4	Negative	Anti-SSA	Negative	0/1
UCTD	F/42	Arthralgia, xerostomia, keratoconjunctivitis sicca	<5 mm	Anti-TPO, 209 Anti-Tg, 150	Speckled	Negative	Negative	0/0
UCTD	F/68	Arthritis, xerostomia, keratoconjunctivitis sicca	<5 mm	Anti-TPO, 19.1	Speckled	Negative	Negative	0/0
UCTD	F/50	Arthralgia, keratoconjunctivitis sicca	<5 mm	Anti-TPO, 30	Speckled	Anti-R052	Negative	0/0
Control	F/22	Xerostomia, keratoconjunctivitis sicca Raynaud's phenomenon	<5 mm	Anti-TPO, 21.2	Negative	Negative	Negative	0/0
Control	F/31	Arthralgia, xerostomia, keratoconjunctivitis sicca	<5 mm	Anti-Tg, 39.7	Negative	Negative	Negative	0/0

UCTD, undifferentiated connective tissue diseases; ATA, anti-thyroid antibodies; anti-TPO, anti-thyroid peroxidase antibody; anti-Tg, anti-thyroglobulin antibody; ANA, antinuclear antibody; ENA, extractable nuclear antigens; RF, rheumatoid factor; F, focus; G, grade

Table 4. Demographic, clinical and laboratory features of UCTD patients without ATD and ATD patients

	UCTD patients without ATD (n=45)	**ATD (n=36)**	**P**
Age, years, mean ±SD	40.90±12.90	43.06±11.10	NS
Gender (female), (%)	40 (88.90)	34 (94.40)	NS
Clinical features, (%)			
Arthralgia	34 (75.60)	18 (50)	0.017
Arthritis	5 (11.10)	1 (2.80)	NS
Xerostomia	23 (51.10)	15 (41.70)	NS
Keratoconjunctivitis sicca	16 (35.60)	11 (30.60)	NS
Oral aphthous ulcers	8 (17.80)	6 (16.70)	NS
Raynaud's phenomenon	2 (4.40)	5(13.90)	NS
Photosensitivity	1 (2.20)	2 (5.60)	NS
Thyroid function, (%)			
Euthyroid	42 (93.30)	17 (47.20)	<0.001
Hypothyroid	3 (6.70)	12 (33.30)	0.002
Hyperthyroid	0	7 (19.40)	0.002
ANA positivity (%)	43 (95.60)	19 (52.80)	<0.001
ANA pattern, (%)			
Nuclear speckled	20 (48.90)	8 (22.20)	<0.001
Nucleolar	12 (26.60)	1 (2.80)	
Homogenous	8 (17.80)	2 (5.60)	
Dense fine speckled	1 (2.30)	7 (19.40)	
Nuclear envelope	1 (2.30)	1 (2.80)	
Nuclear dot	1 (2.30)	0	
RF positivity, (%)	3 (7)	0	NS
CRP, mean ±SD	2.62±3.80	2.25±4.72	NS
C3, mean ±SD	1.15±0.32	1.13±0.40	NS
C4 mean ±SD	1.00±4.39	0.24±0.07	NS

UCTD, undifferentiated connective tissue diseases; ATD, autoimmune thyroid disease; SD, standart deviation; ANA, antinuclear antibody; RF, rheumatoid factor; CRP, C-reactive protein; C3, complement 3; C4, complement 4; NS, not significant.

Discussion

Nowadays, it is now well known that organ-specific and non-organ-specific autoimmune diseases may coexist due to common genetic and possible environmental factors. Particularly, the association of ATD with classified connective tissue diseases, such as SS, RA and SLE has been reported.[1-3] The association of UCTDs with ATD, which are one of the most common patient groups in the rheumatology clinics, remains unclear. In addition, there is no sufficient data on predictive factors necessary to make a differential diagnosis of these two diseases that have many common clinical symptoms and laboratory findings. Only one study has shown the relationship

between UCTD and ATD, in which the prevalence of ATD in UCTD was 6.66%.[13] The present study found a higher prevalence rate (23.70%) for ATD among UCTD patients.

As one of the most significant and common findings of UCTD, joint involvement can be seen in organ-specific autoimmune diseases and hormonal disorders as well as systemic rheumatic diseases. Arthralgia and arthritis can develop in 18.70%–98% and 18.70%–26% of ATD patients, respectively.[1,14] The incidence of non-inflammatory arthritis is increased, and arthritis findings regress with the normalisation of TSH levels following thyroid hormone replacement therapy in the knee, proximal interphalangeal joints, and metacarpophalangeal and metatarsophalangeal joints in case of hypothyroidism.[15,16] In recent years, it has been shown that polyarthralgia may develop in euthyroidism associated with positive thyroid autoantibodies or hypothyroidism independent of any rheumatic disease in ATD, and there is a significant relationship between the number of joints involved and anti-microsomal antibody, erythrocyte sedimentation rate, and TSH levels.[8,14] In the study by Danieli *et al*. on UCTDs, arthritis developed in 4 of 5 hypothyroidic ATD patients.[13] In this study, the prevalence of arthralgia was higher in UCTD patients than in control subjects, and coexisting ATD had no significant effect on arthralgia. In addition, the prevalence of arthritis in the UCTD group was higher among ATD patients (35.70%) than among those without ATD (11.10%), whereas there was no significant difference between ATD and non-ATD patients in the control group. Examination of the relationship between joint involvement and thyroid functions revealed that among 12 patients with arthritis, only 1 UCTD patient had hypothyroidism and the remaining 11 patients (9 UCTD, 2 control) had euthyroidism. However, among 17 patients with hypothyroidism (4 UCTD, 13 control), only 1 UCTD patient had arthritis.

Dry mouth, which is very common in autoimmune diseases such as SS, UCTD, and diabetes mellitus, has been observed in 14%–88.20% of ATDs.[3,17] Studies have shown that salivary gland functions detected by salivary gland scintigraphy are lower in ATD patients with the dry mouth than in ATD patients and healthy individuals without dry mouth.[18,19] In another study, the comparison between ATD patients with dry mouth and healthy individuals revealed that the unstimulated salivary flow rate was significantly decreased, whereas the stimulated salivary flow was decreased but not significantly.[20] In the histopathological examination of salivary gland specimens by Warfvinge *et al*. in 19 ATD patients, 5 patients had autoimmune sialadenitis (more than one lymphocyte focus of ≥50 cells per 4 mm^2) and 3 met the SS criteria, and it was consequently stated that salivary glands are involved in ATD patients to a great extent because of common mechanisms that play a role in the development of autoimmune diseases involving the thyroid and salivary glands.[21] In the present study, the subjective evaluation of dry mouth revealed that although the prevalence of dry mouth in UCTD patients was significantly higher (52.50%) than that in control subjects (31.50%), it was not affected by ATD in both groups. In addition, no evidence of sialadenitis was detected in the examination of salivary glands in 9 ATD patients.

Another common finding observed in UCTD is keratoconjunctivitis sicca. The rate of dry eye complaint in ATD patients has been reported to be 13%–68.80%; however, in patients with Hashimoto's thyroiditis, the ocular surface disease index was significantly high, and Schirmer and tear break up time (TBUT) tests were significantly low.[14,17,22] In the present study, the complaint of dry eye was similar not only in UCTD or isolated

ATD patients (30.60%) but also in a group of patients with no autoimmune disease (30.60%).

ANA, a non-organ-specific autoantibody, is highly positive in ATD patients (45%–50.80%).[5,23] Although there are limited data on other autoantibodies in ATDs, RF (34.40%), anti-dsDNA (18%), anti-Ro/SSA, and anti-La/SSB (14.80%) were positive, and anti-Ro-52 (10%), anti-RNP (14.80%), anti-centromere (1.60%), and anti-DFS (51.80%) were positive in patients testing positive for ANA.[5,24,25] In the study by Danieli *et al.*, ANA (6/6), RF (3/6), and anti-RNP (2/6) antibodies were positive in 6 UCTD and ATD patients, and the staining pattern was homogeneous in 5 patients and speckled in 1 patient with ANA positivity.[13] In the present study, ANA positivity was significantly higher in UCTD patients than in the control group and was similar between isolated ATD patients (52.80%) and those with no autoimmune diseases (41.70%). Different from the previous study, the most common ANA staining patterns in the present study's UCTD and ATD patients were speckled (69.20%) and nucleolar (23.10%), whereas the most common patterns in isolated ATD patients were speckled (22.20%) and nuclear dense fine speckled (19.40%).

ATD and connective tissue diseases have similar symptoms and findings. Therefore, it is sometimes difficult to differentiate findings attributed to ATDs from those associated with connective tissue disorders accompanied by ATD.[17,21] In the study by Milic *et al.*, ATD patients with SS and those with dry mouth were compared and the prevalence of symptoms, such as dry mouth and eyes, dysphagia, Raynaud's phenomenon, arthralgia, and arthritis, was found to be similar.[17] In the present study, the comparison of isolated UCTD patients with ATD patients revealed that arthralgia and ANA positivity were significantly higher in the UCTD group and that of other clinical symptoms were similar. ANA staining patterns were speckled, nucleolar, and homogeneous in isolated UCTD patients, whereas they were speckled and nuclear dense fine speckled in ATD patients.

This is the first study to compare clinical and autoimmune profiles of UCTD and ATD patients, but the lack of a healthy control group is a significant drawback of the study. Furthermore, because ANA dilution was not studied in some patients, particularly in the control group, no observations could be made on this issue.

As a result of this study, majority of the clinical symptoms of UCTD and ATD were similar, but there was a higher rate of ANA positivity in the UCTD group as well as some differences in staining patterns. In UCTD patients, although coexisting ATD could increase the risk of arthritis, it had no significant effect on symptoms such as xerostomia, keratoconjunctivitis sicca, oral aphthous ulcers, and Raynaud's phenomenon. Other clinical symptoms were not affected by thyroid function, except oral aphthae, which are more common with hyperthyroidism.

In conclusion, considering similar clinical symptoms and autoimmune profiles of UCTD and ATD, it is recommended to make a clear differential diagnosis of both diseases in patients presenting with complaints such as arthralgia, xerostomia, and Raynaud's phenomenon, and it must be kept in mind that both diseases can be simultaneously observed.

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