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ORIGINAL ARTICLE

Tumor-Associated Antigens in Rheumatoid Arthritis Interstitial Lung Disease or Malignancy?

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ABSTRACT

Objectives: This study aims to evaluate the serum tumor-associated antigen (TAA) levels and the possible association between these markers and interstitial lung disease (ILD) or malignancy in rheumatoid arthritis (RA) patients.

Patients and methods: The study included 83 RA patients (20 males, 63 females; mean age 59.3±12.1 years; range 25 to 83 years), 43 with ILD (13 males, 30 females; mean age 60.1±11.5 years; range 25 to 83 years) and 40 without ILD (7 males, 33 females; mean age 58.5±12.7 years; range 28 to 78 years). Clinical symptoms, pulmonary function test, chest X-ray, and high-resolution computed tomography were used for the diagnosis of ILD. Age, sex, history of smoking, acute-phase reactants, rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP), carcinoembryonic antigen (CEA), cancer antigen (CA) 15-3, CA 125, and CA 19-9 were evaluated. The relationship between parameters in RA patients with/without ILD was assessed by t-test and Mann-Whitney U test.

Results: Five RA patients (11.6%) with ILD had CEA levels above the upper limit. The numbers of RA-ILD patients with above the upper limit of CA 19-9, CA 15-3, and CA 125 levels were 10 (23.2%), 13 (30.2%), and five (11.6%), respectively. Rates of RA patients without ILD with TAAs exceeding the upper limit were 15% for CEA, 2.5% for CA 19-9, 7.5% for CA 15-3, and 7.5% for CA 125. No evidence of any malignancy was detected by medical history, physical examination, and laboratory and imaging methods in patients who had high levels of serum TAA. CA 15-3 (p=0.001), CA 125 (p=0.040), and CA 19-9 (p=0.018) levels were statistically significantly different in RA patients with ILD compared to those without ILD. RF, CCP, and TAAs were higher in RA patients with ILD than those without ILD.

Conclusion: There is a relationship between ILD and tumor marker levels in connective tissue diseases. Elevated tumor markers may not be associated with hidden tumor or malignancy in RA patients. These antigens may be used as predictive biomarkers particularly in RA patients with ILD.

Keywords: Interstitial lung disease; malignancy; rheumatoid arthritis; tumor-associated antigen.

Rheumatoid arthritis (RA) is a chronic autoimmune systemic disease characterized by the symmetric involvement of small and medium-sized joints. Extraarticular manifestations such as hematologic, cutaneous, ocular, cardiac, pulmonary, and neurological involvement may occur in RA patients.[1] The prevalence of pulmonary involvement varies due to differences in studied populations, study design, and lacking standardized algorithms for the diagnosis of lung involvement. According to a large survey study, interstitial lung disease (ILD) is the most common type of pulmonary involvement with a prevalence of 4.5%.[2] The most common pattern of RA-ILD is usual interstitial pneumonia subtype characterized with bilateral subpleural basal reticulations and honeycombing on high-resolution computed tomography (HRCT), and non-specific interstitial pneumonia with predominant ground-glass abnormalities.[3]

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Tumor markers are biochemical molecules produced by tumoral or normal tissues.[4] Tumor-specific antigens are unique antigens that are not excreted by normal tissues and other tumors, they are encoded by gene products expressed differently by tumors. They may be derived from any protein/glycoprotein produced by the tumor cell, can be cytoplasmic, nuclear, membrane dependent or secreted. TAAs can be categorized on the molecular basis as oncofetal, oncoviral, overexpressed/accumulated, cancer-testis, lineage-restricted, mutated, posttranslationally altered or idiotypic.[5] The association between tumor markers and connective tissue diseases such as systemic lupus erythematosus (SLE), RA, Sjögren's syndrome (SjS), and systemic sclerosis (SSc) was reported in many studies.[6-9] Tumor markers may be elevated in RA patients even with low inflammatory activity and may not indicate the presence of cancer.[10] Also, increased cancer antigen (CA) 19-9 levels were reported in rheumatic diseases as a useful marker for interstitial pneumonia.[11] Additionally, tumor markers were within normal range except CA 125 in a RA patient diagnosed with ovarian adenocarcinoma on the follow-up.[10]

The relationship between TAAs and clinical features in RA patients remains uncertain and the relevant data are still lacking. Therefore, in this study, we aimed to evaluate the serum TAA levels and the possible association between these markers and ILD or malignancy in RA patients.

PATIENTS AND METHODS

Eighty-three RA patients (20 males, 63 females; mean age 59.3±12.1 years; range 25 to 83 years), 43 with ILD (13 males, 30 females; mean age 60.1±11.5 years; range 25 to 83 years) and 40 without ILD (7 males, 33 females; mean age 58.5±12.7 years; range 28 to 78 years), who were referred to Adnan Menderes University Rheumatology clinic between January 2014 and October 2017 were enrolled in this study. The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria were used for the diagnosis of RA.[12] The diagnosis of ILD was established on the basis of clinical symptoms about the respiratory system, pulmonary function test, chest X-ray, and HRCT. We excluded patients with any connective tissue disease other than RA, tuberculosis or any respiratory infections. The study protocol was approved by the Adnan Menderes University Faculty of Medicine Ethics Committee (approval number 2017/1248). A written informed consent was not obtained from the patients due to the retrospective nature of this study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Clinical, laboratory, and radiological data were obtained from patients' records, retrospectively. The following parameters were evaluated: age, sex, history of smoking, diagnosis of any malignancies, acute-phase reactants (sedimentation, C-reactive protein [CRP]), serology (anti-cyclic citrullinated peptide [anti-CCP], rheumatoid factor [RF]), and TAAs such as carcinoembryonic antigen (CEA), CA 15-3, CA 125, and CA 19-9. The normal

Table 1. Demographic characteristics and inflammatory markers of rheumatoid arthritis patients with or without interstitial lung disease

	RA-ILD (n=43)				RA (n=40)				
	n	Mean±SD	Median	25-75 percentile	n	Mean±SD	Median	25-75 percentile	*p*
Age (year)		60.1±11.5				58.5±12.7			0.602
Sex									0.327
Male	13				7				
Female	30				33				
Smoking	5				4				0.827
Sedimentation (mm/h)			70	52-85			64.5	39-87.2	0.639
C-reactive protein (mg/L)			21.4	10-66			26.9	11-59.9	0.610
Rheumatoid factor (IU/mL)			35.9	8.5-124.8			7.6	2.0-60.4	0.054
Anti-CCP (U/mL)			19.5	1.8-140.8			6.2	0.5-125.9	0.209

RA: Rheumatoid arthritis; ILD: Interstitial lung disease; SD: Standard deviation; Anti-CCP: Anti-cyclic citrullinated peptide.

Table 2. The frequency of above upper limit of CEA, CA 15-3, CA199, CA 125 and CA 19-9 in rheumatoid arthritis patients with and without interstitial lung disease

	Rheumatoid arthritis-interstitial lung disease (n=43)		Rheumatoid arthritis		
	n	%	n	%	*p*
Carcinoembryonic antigen	5	11.6	6	15	>0.05
Cancer antigen 15-3	13	30.2	3	7.5	0.012
Cancer antigen 125	5	11.6	3	7.5	>0.05
Cancer antigen 19-9	10	23.2	1	2.5	0.008

CEA: Carcinoembryonic antigen; CA: Cancer antigen; RA: Rheumatoid arthritis.

limits of TAAs are as follows: CEA: 0-5 ng/mL, CA 15-3: 0-31 U/mL, CA 125: 0-35 U/mL, and CA 19-9: 0-37 U/mL.

Statistical analysis

All data were analyzed using the PASW for Windows version 17.0 (SPSS Inc., Chicago, IL, USA). The results were given and expressed as mean±standard deviation. The Student's t-test was utilized to assess whether the differences were significant or not. Mann-Whitney U test was used to compare the differences between groups, and chi-square test was used for categorical comparison. The results were evaluated in 95% confidence interval and a *p* value <0.05 was accepted as statistically significant.

RESULTS

The ratios of female-to-male RA patients were 2.3 and 4.7 in patients with or without ILD, respectively. The parameters such as the level of RF, anti-CCP, mean age, and smoking rate were higher in RA patients with ILD compared to those without ILD. There was no statistically significant difference between smoking rate and TAAs in RA patients. RF was positive in 58.1% of RA patients with ILD and in 45% of RA patients without ILD. The demographic and laboratory features of RA patients with or without ILD were summarized in Table 1.

The mean and median levels of TAAs were higher in RA patients with ILD compared to those without ILD. Five RA patients (11.6%) with ILD had CEA levels above the upper limit. The number of RA-ILD patients with above the upper limit of CA 19-9, CA 15-3, and CA 125 levels were 10 (23.2%), 13 (30.2%), and five (11.6%), respectively. The rates of patients with TAAs exceeding the upper limit in RA patients without ILD was 15% for CEA, 2.5% for CA 19-9, 7.5% for CA 15-3, and 7.5% for CA 125. The frequency of above upper limit of CEA, CA 15-3, CA19-9, CA 125, and CA 19-9 levels in RA patients with or without ILD are shown in Table 2. The levels of CA 19-9, CA 125, and CA 15-3 were significantly higher in RA patients with ILD (p=0.01, p=0.04, and p=0.001, respectively). There was no significant difference between RA patients with ILD and RA patients without ILD in terms of CEA levels. TAAs levels of RA patients with or without pulmonary involvement were summarized in Table 3. No evidence of any malignancy was detected by medical history, physical examination, and laboratory and imaging methods in patients who had high levels of TAAs.

Table 3. Comparison of tumor-associated antigens in rheumatoid arthritis patients with or without pulmonary involvement

	RA-ILD (n=43)			RA (n=40)			
	Mean±SD	Median	25-75 percentile	Mean±SD	Median	25-75 percentile	*p*
Carcinoembryonic antigen (0-5 ng/mL)	2.9±1.6			2.7±1.8			>0.05
Cancer antigen 15-3 (0-31 U/mL)		20.4	15.2-35.1		14.7	8.3-19.6	0.001
Cancer antigen 125 (0-35 U/mL)		18.1	11.5-26.8		12.8	9.2-21.8	0.040
Cancer antigen 19-9 (0-37 U/mL)		11.9	5.6-29.5		7.3	3.7-11.9	0.018

RA: Rheumatoid arthritis; ILD: Interstitial lung disease; SD: Standard deviation.

Table 4. Correlation between tumor-associated antigens and levels of inflammation markers, and autoantibodies in RA patients with interstitial lung disease

	Carcinoembryonic antigen	Cancer antigen 19-9	Cancer antigen 15-3	Cancer antigen 125
Sedimentation	0.120	0.001	0.012	0.016
C-reactive protein	0.198	0.166	0.170	0.012
Rheumatoid factor	0.107	0.023	0.224	0.150
Anti-cyclic citrullinated peptide	0.001	0.239	0.091	0.014
Carcinoembryonic antigen		0.138	0.338*	0.257
Cancer antigen 19-9			0.160	0.239
Cancer antigen 15-3				0.436*

* $p<0.05$, Pearson's correlation coefficient.

A correlation analysis between the levels of tumor antigens revealed a significant correlation between CEA and CA 15-3 ($r=0.33$, $p<0.05$), CA 125, and CA 15-3 ($r=0.43$, $p<0.05$) levels in RA patients with pulmonary involvement. Levels of anti-CCP correlated with RF ($r=0.45$, $p<0.05$). An evaluation of patients without pulmonary involvement showed a correlation between CA 125 and RF ($r=0.43$, $p<0.05$), also a correlation between CA 125 and anti-CCP ($r=0.4$, $p<0.05$). The correlation between TAAs and levels of inflammation markers and autoantibodies in RA patients with ILD were shown in Table 4.

DISCUSSION

Our study aimed to identify the relationship between TAAs and lung involvement, in association with autoantibodies, inflammation markers, and smoking in patients with RA, a systemic autoimmune connective tissue disease. In our study, TAAs were found to be above the normal limit in 31 patients. Twenty of these patients had pulmonary involvement. In the control group without pulmonary involvement, tumor markers were elevated in 11 patients.

Smoking, male sex, longstanding disease, human leukocyte antigen-DR 4, high RF, and anti-citrullinated protein antibody titers, drugs such as methotrexate, leflunomide, and sulfasalazine are risk factors for ILD in patients with RA.[3,13] Early diagnosis is critical due to its poor prognosis, morbidity, and mortality. There is no specifically defined biomarker for predicting ILD in patients with RA. Studies have been reported on biomarkers that may predict early pulmonary involvement in patients with connective tissue diseases and RA.[14-17] It is considered that tumor markers may be associated with low inflammatory activity and pulmonary involvement of rheumatic diseases.[10] Therefore, the association of tumor markers with lung involvement in rheumatic diseases is a research topic. We aimed to determine this possible relationship in this study.

It is well-known that very few tumor markers are specific to particular cancer types.[4,18] CEA is an oncofetal protein also known as cluster of differentiation 66, which may have an important role as a cell-adhesion molecule.[19] Increased CEA levels have been reported in chronic liver disease, adenocarcinomas of digestive organs, colitis, and in smokers.[18] CA 15-3, CA 19-9, and CA 125 are glycoprotein antigens, associated with many cancer types and various benign conditions. Previous studies have shown increased serum and synovial CEA in RA patients.[9,19,20] CA 15-3 was demonstrated to be elevated in RA patients compared to healthy controls.[10,21] In another study, CA 19-9 and CA 125 levels were evaluated in 27 females with collagen tissue diseases and 11 healthy females. In that study, elevated CA 125 was detected in a patient with pleural effusion diagnosed with SSc.[8] We found high levels of tumor markers in 31 of 83 RA patients included in our study. Compared to patients with or without pulmonary involvement, CA 15-3 and CA 19-9 were statistically significantly different between RA patients with ILD and RA patients without ILD (Table 3).

Szekanecz et al.[9] investigated the association between disease activity, organ involvement, and TAA levels (CEA, CA 15-3, CA 19-9, CA 72-4, and CA 125) in patients with infectious diseases, SLE, and SSc. There was a statistically significant difference for levels of CEA and CA 15-3 in SSc patients compared to healthy controls. In this

study, a correlation was found between CA 15-3, CEA, and CA 19-9 levels with renal involvement in SSc patients, CA 72-4 levels with central nervous involvement, and CA 125 levels with Systemic Lupus Erythematosus Disease Activity Index in SLE patients.[9] Also, a correlation between CEA levels and RF positivity has been reported.[10,22] TAAs may play an important role in intercellular adhesions underlying synovial inflammation in RA and have a prognostic importance.[22] We examined the association between lung involvement and tumor markers in our patients. Tumor marker levels were not correlated with inflammatory markers in our RA patients. There was a correlation between CA 125 levels and RF and anti-CCP levels in RA patients without pulmonary involvement (p=0.009 and p=0.005, respectively).

Serum CA 19-9 levels have been evaluated in 47 patients with the diagnosis of RA, SjS, SLE, SSc, mixed connective tissue disease (MCTD), polymyositis/dermatomyositis (PM/DM), polymyalgia rheumatic, and giant cells arteritis.[4] Persistent CA 19-9 elevation was detected in six patients (two with Sjögren's syndrome, two with MCTD, and two with PM/DM). Only one of these patients had pancreatitis, while the remaining five had pulmonary involvement.[7] According to our study, CA 19-9 level was above the normal limits in 10 of RA-ILD patients and in only one of the RA patients without ILD. The mean of CA 19-9 level was 11.9 U/mL in RA patients with ILD, whereas it was 7.3 U/mL in RA patients without ILD, with a statistically significant difference between the two groups (p=0.018) (Table 3).

We detected no malignancy during our patients' follow-up. In the literature, increased serum CA 19-9 was reported in 33.3% of RA patients, 31.6% of SLE patients, and 33.3% of progressive SSc patients without any malignancy.[6] Therefore, it is considered that increased CA 19-9 levels might be related to the pulmonary involvement of inflammatory diseases.[7,11] Although we have not detected any malignancies in our patients with RA, a study reported pancreatic mucinous cystadenocarcinoma without elevated tumor marker and ovarian adenocarcinoma with elevated CA 125 in RA patients during follow-up.[10] In a meta-analysis on the assessment of RA-associated malignancy risk, an increased risk has been shown for particularly lymphoma and lung cancer, as well as a potential risk reduction in colorectal cancer and breast cancer.[23,24] The increased risk of cancer is linked to long-term disease, the severity of disease, seropositivity, ongoing inflammatory activity, and immunosuppressive treatment agents.[25,26] No pancreatic, no ovarian or no any other malignancies were diagnosed in our patients.

Yamamoto et al.[11] suggested an association between serum CA 19-9 level and interstitial pneumonia and diffusing capacity of carbon monoxide (DLCO) in connective tissue diseases. Assessment of patients with rheumatic diseases (PM/DM, progressive systemic sclerosis, RA) without malignancy revealed that patients with interstitial pneumonia had significantly higher positive levels for serum CA 19-9 compared to those without interstitial pneumonia. In another study, Wang et al.[27] investigated serum levels of CEA, CA 15-3, CA 125, and CA 19-9 in 28 patients with RA-ILD and 83 patients with RA. They reported increased CA15-3, CA125 and CA19-9 in RA-ILD patients compared with RA without ILD patients. Levels of all assessed TAAs were higher in the RA-ILD group compared to those without ILD. Levels of TAAs such as CA 19-9, CA 15-3, and CA 125 in RA-ILD patients were 11.9 U/mL, 20.4 U/mL, and 18.1 U/mL, respectively. Moreover, there was significant difference for CA 19-9 (p=0.018), CA 125 (p=0.04), and CA 15-3 (p=0.001), but not for CEA levels between both groups (Table 3). No malignancy was detected associated with TAAs.

Furthermore, researchers in Yamamoto et al.'s study[11] observed decreased CA 19-9 levels after treatment with immunosuppressive agents. This might be related to metaplastic bronchial glandular cells that produce CA 19-9.

A limitation of our study was that we did not evaluate the changes of TAAs levels in RA patients on the follow-up. In another retrospective study, RA patients were analyzed according to the presence or absence of ILD.[21] There was no significant difference for RF, anti-CCP positivity, or acute phase reactants between both groups. It was found that RA-ILD patients had increased tumor markers such as CA 15-3 and CA 125 and decreased of total lung capacity, inspiratory capacity, and DLCO. There was no statistically

significant difference between smoking rate, sedimentation, CRP, RF, or anti-CCP levels in RA patients with or without pulmonary involvement (Table 1).

In conclusion, tumor markers may have a predictive value for pulmonary involvement in RA, particularly in RA with ILD, which is critical for the prognosis of the patient. Increased tumor marker levels may not be associated with malignancy in RA patients. Pulmonary involvement should be considered in the presence of high levels of TAAs specifically in RA patients.

Declaration of conflicting interests

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